EXHIBIT 1

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

FEDERAL TRADE COMMISSION and THE PEOPLE OF THE STATE OF NEW YORK, by LETITIA JAMES, Attorney General of the State of New York, Plaintiffs, v. QUINCY BIOSCIENCE HOLDING COMPANY, INC., a corporation; QUINCY BIOSCIENCE, LLC, a limited liability company; PREVAGEN, INC., a corporation d/b/a SUGAR RIVER SUPPLEMENTS; QUINCY BIOSCIENCE MANUFACTURING, LLC, a limited liability company; MARK UNDERWOOD, individually and as an officer of QUINCY BIOSCIENCE HOLDING COMPANY, INC., QUINCY BIOSCIENCE, LLC, and PREVAGEN, INC.; and Defendants.	Case No. 1:17-cv-00124-LLS **PRETRIAL DECLARATION OF DEFENDANTS' EXPERT WITNESS DAVID GORTLER. Pharm.D.**

I, David Gortler, hereby state and declare as follows:

1. I have been retained by Defendants Quincy Bioscience Holding Company, Inc., Quincy Bioscience, LLC, Prevagen, Inc., Quincy Bioscience Manufacturing, LLC, and Mark Underwood (collectively, "Defendants") in the above-referenced matter. I submit this declaration in accordance with Rule 4.A(4) of the Individual Practices of Judge Louis L. Stanton to summarize the opinions set forth in my expert report and those that I intended to testify about at trial.

Education and Professional Background

2. I was trained as both a pharmacist and a pharmacologist and have over 20 years of experience in drug development including over 15 years of experience in pedagogy as a didactic professor of drug development, drug safety, Food and Drug Administration (FDA) regulatory affairs, and clinical and non-clinical pharmacology.

3. I received my Doctor of Pharmacy from the University of Arizona, College of Pharmacy in 1998. From 1998-1999, I was a postdoctoral general practice resident with the Columbia Presbyterian Hospital. During that time, I lectured as an assistant instructor at The Rutgers College of Pharmacy. From 1999-2002, I did a Vascular and Cardiovascular Medicine postdoctoral fellowship in the Department of Surgery at the Yale School of Medicine. While I was a Post-Doctoral Research Fellow at Yale, my duties included both clinical trial enrollment and monitoring duties and as that of a basic science bench research scientist in a molecular and cellular biology "wet" research laboratory where I conducted in vitro and in vivo biological experiments, including designing and conducting basic science research projects in both pharmacology and molecular biology and novel research experiments exploring original cellular signaling pathways which had the potential to be modulated via pharmacology. My research has been published in prominent basic science and clinical, peer-reviewed journals. I was additionally responsible for screening and enrolling patients at The Yale-New Haven Hospital into multiple investigational medicine trials and working closely with the investigational drug service of the Yale-New Haven Hospital.

4. From 2002 to 2005, I was employed by Pfizer Inc. as an Investigational Medicine Research Scientist and clinical trial supervisor, where I was involved in the clinical research aspects of drug development and was responsible for designing, implementing and managing the timelines of state-of-the-art clinical pharmacology studies for multiple early and late development

compounds. I personally designed, composed investigational medicine study protocols and study reports for drug safety studies, drug efficacy studies, animal studies, proof-of-concept studies, first-in-human studies, multiple dose studies, food effect studies, dose-escalation studies, drug interaction studies, drug safety studies and bioequivalence studies.

5. From 2004-2008, I was an assistant professor at The Yale University School of Medicine, teaching clinical pharmacology courses to medical students and pharmacology PhD candidates.

6. From 2007-2011, I served at the Food and Drug Administration ("FDA") as a Medical Officer in the Office of Drug Evaluation in the Office of New Drugs. I was the lead clinical reviewer responsible for various safety and efficacy analyses of clinical study proposals, reports, product labeling, New Drug Applications, clinical study protocols and clinical protocol amendments. I also provided expert guidance on drug labeling and the design process by which new drugs are evaluated and become approved for marketing in the United States. I also evaluated new compounds, New Drug Applications, (NDAs) drug application supplements, drug labeling and pre-clinical applications based on FDA guidance documents and the Code of Federal Regulations (CFR) and was directly responsible for evaluating the safety and efficacy of drugs both in pre-clinical development and in marketed products.

7. From 2009 to 2014, I was an associate professor at The Georgetown University School of Medicine and served as a didactic professor of pharmacology.

8. From 2015 to 2020, I conceptualized and founded the world's first "analytical pharmacy" tasked with performing independent quality control testing of finished drug product pharmaceuticals.

9. From 2020 to 2021, I returned to the FDA and was the first pharmacist/pharmacologist to be appointed to serve on the FDA senior executive leadership team, or as senior advisor to the FDA commissioner. During this time, I advised the FDA Commissioner and other members of the FDA Senior Executive Leadership Team on scientific matters including drug and device safety, FDA policy and FDA regulatory affairs, wrote opinion articles, policy recommendations, and composed and spearheaded multiple Presidential Executive Orders at the White House, and spearheaded multiple critical public health initiatives.

10. Since early 2021, I have held the title of "Scholar" at the Ethics and Public Policy Center (EPPC) in Washington, DC where I run the FDA section of EPPC's HHS Oversight and Accountability Project. I regularly opine and write articles relating to matters of public health, pharmacology, drug safety, healthcare policy and FDA policy and regulatory affairs.

11. Throughout my career, I have participated extensively at every level, and in virtually every aspect of drug development. I have authored or co-authored over 60 scientific publications, papers, articles, reviews, clinical protocols and reports and have been interviewed and/or quoted over 100 times by the lay press and news reporters as a recognized authority on pharmacology, drug safety, FDA policy and FDA regulatory affairs.

Summary of Testimony

12. As detailed in my rebuttal expert report dated July 15, 2021, it is my opinion that the report and opinions of Plaintiffs' expert, Jeremy Mark Berg, Ph.D., are fundamentally flawed as they relate to pharmacology; likely because he is not a pharmacologist. It is my expert opinion that Dr. Berg makes factual assertions that are contrary to known pharmacological principles.

A. Basic Pharmacology Concepts and Mechanism of Action

13. As set forth in my rebuttal report, some basic principles of pharmacology are necessary to address Dr. Berg's statements. First, receptor theory relates to interactions between

a drug and/or supplement and receptors. Most, but not all, drugs and supplements exert their effects on the body by interacting with receptors or target macromolecules present on the cell surface, but there are an unknown number of targets drugs and/or supplements may have, which include, but it not limited to, enzymes, voltage-gated channels, and transport proteins.

14. Second, in pharmacological terms, mechanism of action means the specific biochemical effect through which a drug or supplement produces an effect. However, a fully revealed mechanism of action is not required to market dietary supplements like Prevagen®. FDA approval is not required for dietary supplements. In fact, possessing a fully elucidated mechanism of action of a drug is not even necessary to obtain FDA approval for dietary supplements *or* drugs. Today, there are many drugs and supplements for which the mechanism of actions are unknown or not fully elucidated, including aspirin, acetaminophen, ibuprofen, diphenhydramine, and well as many of the common drugs used as antidepressants.

B. Dr. Berg's Report Lacks a Full Understanding of Drug Metabolism and Receptor/Ligand Pharmacology

15. Dr. Berg's report adopts an overly simplified mechanism of action theory when he states that "To have a direct effect on brain cells, the active ingredient in Prevagen would need to be absorbed into the bloodstream and cross into the brain." (Berg ¶ 8.) This is simply not accurate. Dr. Berg fails to consider the very fundamental possibility that metabolized components of Prevagen may be either (1) actively transported; or (2) react with receptors either in the stomach or elsewhere in the mucous membranes GI tract; or (3) elicit a pharmacological signaling cascade from within the stomach; or (4) the possibility that Prevagen does not traditionally act on specific receptors targets at all. Dr. Berg also fails to consider the possibilities that one or more of the individual metabolized components of Prevagen could eventually be transported or absorbed and

interact with receptors in the form of a prodrug or that the mechanism of action of Prevagen could have a multitude of other effects depending on exactly how the molecule is broken up.

C. Prodrugs

16. Dr. Berg also fails to consider the possibility that metabolized components of Prevagen can be activated into pharmacologically active moieties, such that it would meet the definition of a prodrug. Prodrugs are compounds that are inactive in their parent form but following metabolization are chemically transformed into an active drug. Such drugs and supplements need to undergo an enzymatic and/or chemical transformation in vivo to be activated and subsequently have a pharmacological effect. Prodrugs have been known to exist in the natural form for around 100 years, even in compounds which have not been intentionally designed as prodrugs.

17. My rebuttal report provides many of examples of prescription prodrugs currently in use. Indeed, practically every therapeutic category has at least one compound in its class that is a prodrug, including: analgesia, heart disease, anti-infectives, antipyretics, GERD, cancer treatment, blood pressure treatment and high cholesterol treatment. Moreover, many known homeopathic compounds naturally exist in the prodrug form.

D. Prodrugs and Large Molecule Pharmacology

18. Both naturally found and prospectively designed prodrugs may be larger molecules which have the ability to have better absorption, improved delivery or superior efficacy. They exist in an inactive form, and following an enzymatic or other chemical process, are designed to break down inside the body into an active form. This may occur in almost any part of the body, as well as intracellularly or extracellularly.

19. For example, as discussed in my report, the tissue or location of prodrug conversion may occur in metabolic tissues, therapeutic target tissues/cells, GI fluids, and/or systemic circulation and other extracellular fluid compartments. Dr. Berg's failure to consider this possibility underscores his misunderstanding of an important area of pharmacology.

E. Pharmacogenetics/ Pharmacogenomics

20. Pharmacogenetics / Pharmacogenomics (used interchangeably) have been defined as the study of variability in response due to one's specific individual genetic disposition. Genetic variations in human beings may lead to variations in response to food, drugs, or dietary supplements. Thus, pharmacogenomics is viewed as an emerging and critical specialty of its own, and an obviously highly important area for improving drug therapy and prescribing in the future.

21. However, Dr. Berg's report illustrates a perceptibly naïve, outdated, and in my opinion, *fundamentally* incorrect, non-FDA-regulatory level of consideration regarding absorption, distribution, metabolism and excretion. His approach and analysis appears to follow "a one hypothesis fits all" meaning whereby only one modeling methodology will or will not work the same way on everyone, but this ignores very basic and widely accepted and proven pharmacological as well as pharmacogenomic concepts and data that support therapeutic management associations as well as variations in metabolism and drug response.

F. Molecule Size

22. Dr. Berg states that "Proteins, in contrast, generally cannot survive digestion in the stomach intact" and cites the larger size of apoaequorin as a factor for its rapid deterioration in the stomach. (Berg ¶¶ 17-18.). However, Dr. Berg fails to consider both the fact that it may be possible for proteins and biologics even larger than apoaequorin to survive the gastric conditions of the stomach and that clinical research has shown us that many larger, complex things -- including

complex biological organisms -- have the potential to survive the enzymatic and chemical conditions in the human stomach.

23. In fact, Dr. Berg's incorrect assertions about the destruction of any 'large protein structure' within the gut is reminiscent of the clinical conflicts that delayed the identification of Helicobacter pylori ("H. Pylori") in 1983. For nearly a century prior, it was incorrectly assumed that the extremely low pH conditions in the stomach made the stomach a "sterile" environment where it was impossible for anything to survive, and that the stomach enzymatically or chemically broken down and/or otherwise inactivated anything that came within its contact. In addition to H. Pylori, large microorganisms that are not digested in the stomach can actually survive and thrive in the stomach, including but not limited to Escherichia Coli, Listeria monocytogenes, Salmonella, Campylobacter, and Clostridium difficile. There are also many viral sources of gastrointestinal causes of infectious diseases including classes of the norovirus, rotavirus, and astrovirus.

24. Thus, Dr. Berg's blanket assertion that Prevagen's active ingredient cannot survive digestion and could never have pharmacological activity in the body merely because of its size is contrary to well-founded pharmacological and other scientific concepts.

G. Active Transport of Prevagen in the Gut and Blood-Brain Barrier

25. Active transport is the body's ability to employ energy to forcibly move molecules across a cell membrane from a region of lower concentration to a region of higher concentration, against a concentration gradient. Active transport is a well-established cellular biology concept, yet Dr. Berg expresses his disagreement with this established and scientifically proven concept.

26. Published data has shown that the dietary intake of apoaequorin together with dietary cholesterol has the potential to "greatly facilitate" the uptake of intact protein from the gut. Published, peer-reviewed modeling studies indicate that the presence of a CARC or CRAC motif

in a protein usually indicates its intrinsic capability to interact with cholesterol. Notably, Prevagen contains at least four of these separate and distinct cholesterol-binding sites to bind cholesterol which can assist with active transport into the blood stream or into the brain. Although, the mechanism of action of Prevagen is unknown, published findings state that cholesterol binding may facilitate Prevagen's uptake across the blood-brain barrier and/or entry into cells of the hippocampus where it is known to elicit a clinical effect through its effect on calcium signaling. That further suggests that the apoaequorin/cholesterol complex may be taken up by hippocampal neurons and serve to facilitate memory consolidation.

27. Stated more simply, any dietary or circulating cholesterol could assist in actively transporting Prevagen through the gut and into the brain. It is possible that either of these pathways relating to the mechanism of action is worth exploring, but Dr. Berg's categorical assertion that Prevagen cannot work is unsupported by published scientific evidence.

H. Fundamental Concepts of Calcium Signaling and Memory

28. The role of calcium in neurological modalities is widely recognized by a great abundance of scientific publications. Since calcium homeostasis dysfunction far precedes any visible changes in brain volume, and calcium has a clearly established role throughout the literature, it seems only reasonable to attempt to engineer a neuronal calcium-modulating drug to affect downstream cell maintenance and repair.

29. Calcium-binding compounds (like Prevagen) have been prominently recognized as protective factors in neuronal populations susceptible to toxicity via calcium and calcium-mediated events.

I. Memory Physiology

30. One of the most troubling concomitants of aging for many individuals is the impairment of learning and memory which often occurs even with "normal" aging. Neuronal changes occur during aging and contribute to learning and memory deficits. This includes calcium-mediated currents, as related to acquisition of hippocampus-dependent behavioral tasks and to age.

31. I understand that Prevagen is a dietary supplement that is marketed to healthy adults who have concerns about the normal aging process and its potential effect on memory and cognitive functioning. This type of proactive, safe and low-cost therapeutic approach makes good sense given that clinical data suggests that it is safe and does in fact provide benefits.

J. Non-Clinical (Animal) Studies

32. Based on in vitro and in vivo animal studies involving apoaequorin in addition to other studies involving large proteins that bind calcium there is scientific potential to enhance memory and cognitive function in humans via calcium binding. Controlled studies over a 32-day period with apoaequorin in aged canines also demonstrated a statistically significant cognitive enhancement. Moreover, pretreatment with apoaequorin specifically has been reported to protect the rat brain slice hippocampal neurons from oxygen-glucose deprivation and has led to studies of the effects of an oral supplement containing apoaequorin on verbal learning in older humans.

K. Memory and Calcium Signaling

33. One hypotheses for the cause of cognitive decline involve the dysregulation of calcium in the hippocampus. Prevagen and/or its substrates and/or its metabolites may exert pharmacological activity through calcium signaling binding sites. In terms of calcium binding sites, cholesterol binding domains and pore lining regions -- the active ingredient in Prevagen (apoaequorin) -- is very similar to calmodulin, (a intracellular multifunctional intermediate

calcium-binding messenger protein) which plays a primary factor in memory consolidation. Apoaequorin has been shown in preliminary laboratory study to decrease cell death due to ischemia by 55% in aged hippocampal cells, ostensibly via calcium signaling, but possibly through another mechanism.

34. Accordingly, various human, animal and basic science studies along with Prevagen's binding sites are indicative of Prevagen having a positive therapeutic utility in delaying or modifying the decline, via calcium buffering or other mechanism, with regards to the cognitive functioning associated with aging.

L. Madison Memory Study Clinical Proof of Concept

35. I have also reviewed and agree with the published findings of the Madison Memory Study (MMS). There are no contradicting published clinical studies that I found during a thorough search of Medline. The MMS clinical results demonstrate that Prevagen (apoaequorin 10mg) was statistically significantly better than placebo at improving domains of cognitive function such as learning and delayed recall after 90 days. For adults with memory concerns, Prevagen is a safe, effective and well-tolerated supplement to help with cognitive function. These results suggest adults just beginning to experience some memory lapses may benefit most from Prevagen.

CONCLUSIONS

36. It is my expert scientific opinion, within a reasonable degree of scientific certainty, that Dr. Berg's opinion regarding the lack of evidence is contrary to a great abundance of published, well-established and well-accepted scientific data, and that there exists competent and reliable scientific evidence to support the Challenged Claims (as defined in my rebuttal report) made regarding Prevagen.

37. Age-related memory loss has no convincing FDA-approved pharmacological cure. Existing drug treatments are few and have only been minimally and/or temporarily effective. The

dietary supplement Prevagen appears to be able to be safely administered by the lay public at its recommended doses. Prevagen should be permitted to continue being sold as-is as a nutritional supplement based on its existing in vivo and in vitro findings.

38. Prevagen's potential efficacy, coupled with the published positive statistically significant clinical and non-clinical results, and an entirely plausible pharmacological mechanism of action and putative calcium-connected disease pathology, including the following facts, show that Prevagen is likely to have an efficacious effect: (1) Calcium plays a basic and critical role in learning, and memory in the human brain; (2) Dysregulated, excess neuronal/hippocampal calcium has objectively been shown in the literature whether by cause or as a biomarker in playing a negative role in memory formation and several memory-related conditions; (3) Prevagen has been shown to have four different calcium binding sites, each of which may work a) in combination or b) separately to bind excess calcium; (4) Prevagen and/or its substrates and/or its metabolites may exert pharmacological activity through calcium signaling binding sites; and (5) Prevagen has the potential to be actively transported in part or whole through a) the gut through or b) into the CNS via active transport via its three separate cholesterol binding sites.

39. I intend to rely on the published references and documents set forth in the Appendix to support my opinions at trial.

40. A full copy of the rebuttal expert report I submitted in this Action is attached hereto as Exhibit A.

I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct.

Executed on September __, 2022 in _____.

D. Gortler

Digitally signed by D. Gortler
Date: 2022.09.12 16:06:14 -07'00'

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David Gortler, Pharm. D.

APPENDIX

2018 FDA approvals. https://www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products/novel-drug-approvals-2018

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EXHIBIT A

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

FEDERAL TRADE COMMISSION and THE PEOPLE OF THE STATE OF NEW YORK, by LETITIA JAMES, Attorney General of the State of New York, Plaintiffs, v. QUINCY BIOSCIENCE HOLDING COMPANY, INC., a corporation; QUINCY BIOSCIENCE, LLC, a limited liability company; PREVAGEN, INC., a corporation d/b/a/ SUGAR RIVER SUPPLEMENTS; QUINCY BIOSCIENCE MANUFACTURING, LLC, a limited liability company; and MARK UNDERWOOD, individually and as an officer of QUINCY BIOSCIENCE HOLDING COMPANY, INC., QUINCY BIOSCIENCE, LLC, and PREVAGEN, INC., Defendants.	Case No. 1:17-cv-00124-LLS

REBUTTAL EXPERT REPORT OF DAVID GORTLER, Pharm.D.

I. QUALIFICATIONS AND SCOPE

1. I have been retained by Defendants Quincy Bioscience Holding Company, Inc., Quincy Bioscience, LLC, Prevagen, Inc., Quincy Bioscience Manufacturing LLC (collectively "Quincy") and Mark Underwood (with Quincy, "Defendants") to review the expert Report of Jeremy Mark Berg, Ph.D. submitted in *Federal Trade Commission, et al. v. Quincy Bioscience Holding Company, Inc. et al.*, Case No. 1:17-cv-001124 (S.D.N.Y.) and respond to certain opinions and statements made by him.

2. Specifically, I have been retained to respond to Dr. Berg's statements from the perspective of a pharmacologist and to determine whether there is a reasonable basis for Defendants to make following claims with respect to Prevagen®/apoaequorin ("Prevagen"): (i) Improves memory; (ii) Improves memory within 90 days; (iii) Reduces memory problems associated with aging; (iv) Provides and/or supports other cognitive benefits, including: (a) Healthy brain function; (b) Sharper mind; and (c) Clearer Thinking (all of which are referred to in this report as the "Challenged Claims").

3. After reviewing the scientific evidence, which includes studies and other literature relating to apoaequorin and Prevagen, and my own academic training and professional experience, it is my opinion that Dr. Berg's report is fundamentally flawed when it relates to pharmacology. That is most likely because he is not a pharmacologist and, therefore, makes factual assertions that are contrary to known pharmacological principles.

4. I was trained as both a pharmacist and a pharmacologist and have over 20 years of experience in drug development including over 15 years of experience in pedagogy as a didactic professor of drug development, drug safety, Food and Drug Administration (FDA) regulatory

affairs, clinical and non-clinical pharmacology. I am an expert in drug safety and on the laws, regulations and rules of the United States FDA. I have authored or co-authored over 60 scientific publications, papers, articles, reviews, clinical protocols and reports.

5. I have been interviewed and/or quoted over 100 times by the lay press and news reporters working for both major newspapers and magazines/periodicals, as well as by specialty news publications as a recognized authority on pharmacology, drug safety, FDA policy and FDA regulatory affairs.

6. I have also been invited to testify in front of the United States Senate on matters relating to FDA policy and drug safety.

7. I have served as the Healthcare/ FDA regulatory affairs and FDA policy advisor to both a U.S. president and a U.S. presidential candidate. I have also served at the FDA under a total of three different presidential administrations.

8. From 1998-1999, I was a postdoctoral general practice resident with the Columbia Presbyterian Hospital. During that time, I lectured as an assistant instructor at The Rutgers College of Pharmacy.

9. From 1999-2002, I did a Vascular and Cardiovascular Medicine postdoctoral fellowship in the Department of Surgery at the Yale School of Medicine. During my research fellowship, I held the title of "Post-Doctoral Research Fellow." My duties included both clinical trial enrollment and monitoring duties and as that of a basic science bench research scientist in a molecular and cellular biology "wet" research laboratory where I conducted *in vitro* and *in vivo* biological experiments.

10. My research included designing and conducting basic science research projects in both pharmacology and molecular biology in a Yale University School of Medicine laboratory. I conducted novel research experiments exploring original cellular signaling pathways which had the potential to be modulated via pharmacology. Projects included exploring the molecular mechanisms of hypertension and diabetes in association with cholesterol plaque initiation, formation, progression and intimal hyperplasia as related to the effects of the repetitive pulsatile circumferential and tangential hemodynamics on the human vasculature due to the beating human heart. I have published my research findings in prominent basic science and clinical, peer-reviewed journals.

11. During my post-doctoral fellowship, I was additionally responsible for enrolling patients at The Yale-New Haven Hospital into multiple investigational medicine trials and working closely with the investigational drug service of the Yale-New Haven Hospital affiliated with Yale University.

12. From 2002-2005 I was employed by Pfizer Inc. as an Investigational Medicine Research Scientist and clinical trial supervisor. At Pfizer, I was involved in the clinical research aspects of drug development and was responsible for designing, implementing and managing the timelines of state-of-the-art clinical pharmacology studies for multiple early and late development compounds. I have personally designed, composed investigational medicine study protocols and study reports for drug safety studies, drug efficacy studies, animal studies, proof-of-concept studies, first-in-human studies, multiple dose studies, food effect studies, dose-escalation studies, drug interaction studies, drug safety studies and bioequivalence studies.

13. At Pfizer, I was also responsible for many aspects of driving forward investigational medicine studies including: CRO negotiations, supervision and management, CRO selection, study initiation, clinical safety monitoring, running study team meetings, and managing a multidisciplinary operational group (including: clinical research associates, project assistants, medical monitors, assay coordinators, biometricians, toxicologists, veterinarians, and data managers). I was also a contributor to Early Clinical Development Plans of early phase compounds and thus, am familiar with the evaluation of the pharmacologic properties of drugs prior to review and approval of the FDA.

14. From 2004-2008, I taught pharmacology as an assistant professor at The Yale University School of Medicine. As a didactic professor at Yale, I taught various graduate, advanced- level basic science and clinical pharmacology courses to medical students and pharmacology PhD candidates.

15. While an assistant professor, I also was involved in multiple interdisciplinary scientific and research collaborations and made multiple academic presentations to students and the medical and research faculty and students. I also served as a faculty member of the Yale University Center for Bioethics, Clinical Trial Ethics Working Group and Research Ethics Writing Group.

16. Thus, I am familiar with and have taught both basic science and advanced scientific principles of clinical- and non-clinical pharmacology, the application to clinical pharmacology and research, and study design aspects of pharmacology. My research has included exploring hemodynamic cell signaling pathways related to components of the vasculature and cell signaling pathways for athero-initiation and atheroprogression.

17. From 2007-2011, I served at the FDA as a Medical Officer (aka, Senior Medical Analyst) in the Office of Drug Evaluation in the Office of New Drugs. While employed by the FDA, I was the lead clinical reviewer responsible for various safety and efficacy analyses of clinical study proposals, reports, product labeling, New Drug Applications, clinical study protocols and clinical protocol amendments. As part of my job as an FDA Medical Officer, I provided the latest expert guidance to major drug companies on drug labeling and the design process by which new drugs are evaluated and become approved for marketing in the United States through the FDA.

18. As an FDA Medical Officer, I evaluated new compounds, NDAs, supplements and pre-clinical applications based on FDA guidance documents and the Code of Federal Regulations (CFR). My major responsibility as an FDA Medical Officer was being directly responsible for evaluating the safety and efficacy of drugs both in pre-clinical development and in marketed products. As part of my job, I personally evaluated drug company data and was in charge of approving new drugs and revising labeling of existing drugs based on the latest clinical and scientific findings.

19. I have prepared full reports as well as given major presentations for interdisciplinary reviewers as well as the entire senior management at the FDA on important matters of public health related to the safety and efficacy of marketed products, including clinical study protocols and proposed changes to drug package labeling/package inserts.

20. My responsibilities at the FDA as a Medical Officer included working with many pharmaceutical companies regarding the safety, efficacy and clinical protocol designs for both pre-clinical and approved products. In this capacity, I advised drug companies on the suitability of

drug development plans and clinical trials, evaluating whether drug company FDA applications for approval were sufficient to support the FDA's CFR requirement for efficacy and safety. On behalf of the FDA, I advised major pharmaceutical companies and academic investigators on the design of clinical studies, ethics, data monitoring and outcome evaluations.

21. From 2009 to 2014, I was an associate professor at The Georgetown University School of Medicine and served as a didactic professor of pharmacology. My responsibilities included thesis advising to graduate level pharmacology and medical students in various therapeutic areas including drug safety, cardiology and metabolic diseases. I was also a research advisor for Medical and Pharmacology PhD students and taught the appropriate methodology and scientific principles for conducting research various disciplines of pharmacology.

22. From 2015 to 2020, I also personally conceptualized and founded the world's first "analytical pharmacy" which was tasked with performing independent quality control testing of finished drug product pharmaceuticals from the USA and overseas.

23. I have served on multiple journal editorial boards of pharmacology, drug safety and investigational medicine journals and have served as the Editor-in-Chief of *Advances in Investigational Pharmacology and Therapeutic Medicine.*

24. From 2020-2021, (second tour of duty at the FDA) I was the first pharmacist/pharmacologist to ever be appointed to serve on the FDA senior executive leadership team, or as senior advisor to the FDA commissioner in the 100+ year history of the FDA.

25. As part of my duties, I advised the FDA Commissioner and other members of the FDA Senior Executive Leadership Team on scientific matters including drug and device safety,

FDA policy and FDA regulatory affairs. I wrote opinion articles, policy recommendations, and composed and spearheaded multiple Presidential Executive Orders at the White House.

26. While on the FDA Senior Executive Leadership team, I spearheaded multiple critical public health initiatives involving eliminating and replacing outdated FDA requirements for animal testing with more modern, state-of-the-art techniques such as organ-on-a-chip (OOC), drug pricing, spread pricing, advanced manufacturing processes, transparency in the origins of consumer prescription drugs, regulation of PBMs, FDA "release testing" of drugs coming from countries with poor inspection histories, better monitoring of drug safety including expansion of AERS/FAERS/MAUDE/VARES safety reporting requirements at the FDA to match those requirements of employees in the pharmaceutical industry, giving the FDA recall authority for any issues involving failing quality control, various regulatory interventions to address the 2019-nCoV opioid increases, fix the broken FDA hiring system which prevents the agency from hiring the brightest and best scientists, having an outside FDA ethics oversight board, and punishing FDA employees for bad regulatory decisions if they were found to negatively impact individuals or public health.

27. As part of my duties, I also worked directly with various members of the White House Senior Executive Service staff and assisted in composing executive orders relating to matters of drug safety, public health and FDA policy.

28. I continue to attend and present research findings at conferences and educate students, physicians and health care professionals on subjects related to pharmacology, investigational medicine, drug safety and FDA regulatory affairs and FDA policy-related matters.

This includes all aspects of clinical trials, drug and device development, and testing and safety monitoring.

29. Since early 2021, I have held the title of "Scholar" at the Ethics and Public Policy Center (EPPC) in Washington, DC where I run the FDA section of EPPC's HHS Oversight and Accountability Project. I am also a columnist for *Forbes*, where I regularly publish original articles on matters of pharmacology, drug safety, FDA policy and FDA regulatory affairs.

30. Over the past two decades, I have participated extensively at every level, and in virtually every aspect of drug development. This includes how drugs may be applied as disease treatment modalities for the responsible improvement of the human condition, the drug evaluation process from pre-clinical testing to post-marketing surveillance, untoward clinical effects, and all phases of drug development (phases 1-4). My work and research in academia, industry, and with the federal government have positioned me as an expert in drug development, drug safety, FDA regulatory affairs and FDA policy. I have been involved in nearly every aspect of the internal FDA review and approval process, the FDA labeling review and approval process, and the identification of the pharmacologic mechanisms whereby drugs can have adverse outcomes on the human body based on their identified mechanism of action.

31. A copy of my curriculum vitae is attached hereto as Exhibit A. I have been compensated at the rate of $600 per hour for my work on this matter.

32. I have not testified as an expert at trial over the past four years, but have given multiple depositions over the past four years.

II. BASIC PHARMACOLOGY CONCEPTS AND MECHANISM OF ACTION

33. To address some of Dr. Berg's statements, it is first necessary to establish some basic principles of pharmacology, which are set forth below.

34. Receptor theory is the principle relating to interactions between a drug and/or supplement and receptors. Drug/supplement–receptor interactions entail the consecutive processes of binding, recognition, and signal transduction throughout the entire human body. Most – but not all – drugs and supplements exert their effects on the body (both beneficial and harmful) by interacting with receptors or target macromolecules present on the cell surface.[1] [2] [3] [4] There are an unknown number of other targets that drugs and/or supplements may have, which include enzymes, voltage-gated channels, transport proteins et cetera. Molecules have the ability to bind to any three-dimensional object within the human body following administration.[5]

35. In pharmacological terms the mechanism of action means the specific biochemical effect through which a drug produces a pharmacological effect.

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[1] Howland, RD, Mycek, MJ. Lippincots Pharmacology, 3rd ed. LWW, Baltimore, MD, 2006 pp25

[2] American Pharmacist's Association Pharmacy Library "The Complete PCOA® Review" Chapter 7: Pharmacology. July 2020. Accessed on 5-28-21 at https://doi.org/10.21019/9781582123417.ch7

[3] Simon Z, Peragovics A, Vigh-Smeller M, et al. Drug Effect Prediction by Polypharmacology-Based Interaction Profiling Journal of Chem Inf Model 2012 52 (1), 134-145

[4] Simon RJ. Pharmacodynamics for the prescriber, Clin Pharm, Volume 48, Issue 7, 2020, Pages 427-432 accessed at: https://www.sciencedirect.com/science/article/abs/pii/S1357303920300815 on 5/28/2021

[5] Golan DE, Tashjian AH, Armstrong EJ. Principles of Pharmcology and the basis of drug therapy. LWW, 2005

36. There are certain drugs where the mechanism of action is believed to be known. Aspirin is one such drug. However, despite its efficacy and popularity, the mechanism of action of aspirin was not known for thousands of years.

37. Just because the mechanism of action is not known does not mean that the drug does not provide a therapeutic effect. Aspirin is a perfect example. Aspirin is a synthetic that is derived from salicylic acid, which is the main component of an extract from tree bark. It is often associated with the bark from willow trees. Humans have used aspirin for thousands of years dating back at least to the Sumerians approximately 4,000 years ago. Since then, ancient and modern peoples have used it as a remedy for pain, fever and inflammation. Aspirin was synthesized around one hundred years ago, however, the mechanism of action was unknown until 1971 when John Robert Vane discovered that aspirin was an inhibitor of prostaglandins and thromboxanes. Despite not understanding the mechanism of action, this popular drug was used by Hippocrates and has functioned as a pain reliever, fever reducer and anti-inflammation and clearly provided a therapeutic effect.

38. It is my understanding that Prevagen is a dietary supplement. Unlike drugs, dietary supplements are not required to be approved by the FDA. However, all FDA approved-drugs are required to have package labeling. Every package labeling section has a section titled clinical pharmacology/mechanism of action. The majority of these sections imply, paraphrase or directly state: "*…the entire mechanism of action is not completely understood*" or "*...however, the complete mechanism of action has not been fully elucidated*" or "*the probable mechanism is…*" or "*this drug appears to work by…*" among other similar statements.

39. Today, doctors regularly prescribe drugs for which the mechanism of action is unknown. In fact, the Physicians' Desk Reference, which is a compilation of information regarding prescription drugs contain many drugs for which the mechanism of action is unknown or not fully understood. Drug labels contain warnings relating to the fact that the mechanism of action is unknown or not fully understood and those drugs include some of the most commonly used prescription and over-the-counter drugs such as: acetaminophen[6] (Tylenol), ibuprofen[7] (Motrin) and diphenhydramine[8] (Benadryl) which are sold individually or in combination in dozens of available pharmaceutical preparations in the United States and worldwide. In addition, the mechanism of action for drugs such as antidepressants; lithium; acamprosate (Campral) (treats alcohol disorder); armodafinil (Nuvigil) (treats daytime sleepiness); Cyclobenzaprine (Flexeril) (treats muscle spasms); demeclocycline (Meciclin) (antibiotic); meprobamate (Miltown) (tranquilizer); paracetamol (acetaminophen) (pain reliever); and metformin (Glucophage) (treats type 2 diabetes) are also unknown or not fully understood.

40. Possessing a fully elucidated mechanism of action of a drug is not necessary to obtain FDA approval. Likewise, a fully revealed mechanism of action is not a requirement for the marketing of *any* dietary supplements, including Prevagen. Rather, all that is required scientifically speaking is "truthful, not misleading, and substantiated" information[9] which may be in the form of basic science or clinical outcomes research. This report provides a basis for the statistical significance, prospective science, proof of concept and positive, statistically significant

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[6] https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/204767s000lbl.pdf

[7] https://www.accessdata.fda.gov/drugsatfda_docs/label/2007/017463s105lbl.pdf

[8] https://meritpharm.b-cdn.net/wp-content/uploads/2019/09/Diphenhydramine.1mL.Insert.pdf

[9] "Dietary Supplements: An Advertising Guide for Industry" ("FTC Guidance") Accessed at: https://www.ftc.gov/tips-advice/business-center/guidance/dietary-supplements-advertising-guide-industry

clinical research findings of Prevagen which substantiates its effect and supports the Challenged Claims.

III. DR. BERG'S REPORT LACKS A FULL UNDERSTANDING OF DRUG METABOLISM AND RECEPTOR/LIGAND PHARMACOLOGY

41. In his report, Dr. Berg uses an overly simplified basis for the mechanism of action of Prevagen when he states that "To have a direct effect on brain cells, the active ingredient in Prevagen would need to be absorbed into the bloodstream and cross into the brain." (Berg ¶ 8.) He fails to consider the very fundamental possibility that metabolized components of Prevagen may be either:

1) Actively transported; or

2) React with receptors either in the stomach or elsewhere in the mucous membranes GI tract; or

3) Elicit a pharmacological signaling cascade from within the stomach; or

4) The possibility the drug does not traditionally act on specific receptors targets at all (per reference numbers 1-4).

5) Furthermore, Dr. Berg neglects to consider the obvious possibility that one or more of the individual metabolized components of Prevagen could eventually be transported or absorbed and interact with receptors in the form of a *prodrug*.

42. The mechanism of action of Prevagen could have a multitude of other effects depending on exactly how the molecule is broken up, or if Prevagen was broken up, depending on a patient's stomach acidity/pH level, a patient's use of prescription or over-the-counter acid relief

agents. The differences of how a patient metabolize drugs can be due to many possible genetic polymorphisms.

43. One of the things that make pharmacology so extraordinary is that even though all human beings are 99.9% (or more) the same, many individuals can metabolize or react very differently to administered foods, supplements, or drugs. For example, one person may take a drug and have no side effects from it at all, and have the drug work perfectly efficaciously, others can have the same drug not be effective, or have a broad multitude of adverse effects up to, and including, hospitalization, temporary disability, permeant disability or even death. Such variation can be responsible for drug response and drug metabolism. This area of interest is one component of a discipline known as *pharmacogenetics and pharmacogenomics.* (see later subsection)

IV. PRODRUGS

44. By design or by nature, some drugs and supplements need to undergo an enzymatic and/or chemical transformation *in vivo* to be activated and subsequently have a pharmacological effect.[10] For example, prodrugs are an established strategy for administering pharmacologically potent compounds and thereby overcoming absorption and size limitation barriers to a drug's developability and usefulness.

45. Prodrugs are defined as compounds that are inactive in their parent form but following metabolization are chemically transformed into an active drug.[11] The concept of a

[10] Rautio J., Kumpulainen H., Heimbach T et al. Prodrugs: design and clinical applications. *Nat Rev Drug Discov* 7, 255–270 (2008).

[11] Waller DG, George CF. Prodrugs. *Br J Clin Pharmocol* 1989, 28 497-507

prospectively engineered prodrug was envisioned over 60 years ago.[12] However, prodrugs have been known to exist in the natural form for around 100 years, even in compounds which haven't been prospectively designed as prodrugs. In fact, the first compound fulfilling the classical criteria of a prodrug was acetanilide, introduced (under the name of Antifebrin®) in Germany in 1867 as an antipyretic agent.[13] Acetanilide is a prodrug activated by the body to what we know today as acetaminophen.

46. By default, prodrugs include compounds which have both active parent structures and/or metabolites which have pharmacological activity. There are many of examples of prescription prodrugs currently used today and they include some of the most commonly used newer and older drugs such as: acetaminophen(Tylenol)[14], tramadol (Ultram)[15], codeine[16], isonioazid (Nydrazid)[17], various progesterone esters[18], spironolactone (Aldactone)[19], nambutone

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[12] Albert A. Chemical aspects of selective toxicitity. *Nature*. 1958

13 Hepp P. Das Antifebrin, ein neues Fiebermittel. Centralbl Klein Med 1886;7:561–564

[14] Bertolini A, Ferrari A, Ottani A et al. Paracetamol: New Vistas of an Old Drug. *CNS Drug Reviews* Vol. 12, No. 3–4, pp. 250–275

[15] Mitto K, Chi AK, Khalil MA. Anesthetic Clinical Pharmacology: Trends in Tramadol: Pharmacology, Metabolism, and Misuse. *Anesth and Analg* January 2017 Volume 124 Issue 1 - p 44-51

[16] Smith H. Opioid Metabolism *Mayo Clin Proc*. 2009 Jul; 84(7): 613–624

[17] Sing AK Kumar RP, Pandey N. Mode of binding of the tuberculosis prodrug isoniazid to heme peroxidases: binding studies and crystal structure of bovine lactoperoxidase with isoniazid at 2.7 A resolution. *J Biol Chem* 2010 Jan 8;285(2):1569-76

[18] Adreen L, Spigset O, Andersson S et al. Pharmacokinetics of progesterone and its metabolites allopregnanolone and pregnanolone after oral administration of low-dose progesterone *Maturitas*. 2006 Jun 20;54(3):238-44

[19] Avataneo V, Dinicola A, Rabbia F et al. A simple UHPLC-PDA method with a fast dilute-and-shot sample preparation for the quantification of canrenone and its prodrug spironolactone in human urine samples. J *Pharmacol Toxicological Meth*. v94, Part 2, November–December 2018, Pages 29-35

(Relafen)[20], sibutramine (Meridia)[21], valcyclovir (Valtrex)[22], tamoxifen (Novaldex)[23], ampicillin (Omnipen)[24], rabeprazole (Aciphex)[25], sulidac (Clinoril)[26], prednisone (Deltasone)[27], mercaptopurine (Purinethol)[28] simvastatin (Zocor)[29]. This brief list is by no means comprehensive because prodrugs likely number in the dozens or hundreds when considering all FDA approved products and therapeutic supplements. However, it illustrates the fact that practically every therapeutic category such as: analgesia, heart disease, anti-infectives, antipyretics, GERD, cancer treatment, blood pressure treatment and high cholesterol treatment has at least one compound in its class that is a prodrug, even though they weren't prospectively chemically designed as such.

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[20] Hender T, Samuelsson O, Wahrborg P et al. Nabumetone: therapeutic use and safety profile in the management of osteoarthritis and rheumatoid arthritis. *Drugs*. 2004;64(20):2315-43; discussion 2344-5

[21] Han S, Jeon S, Hong T at al. Exposure-response model for sibutramine and placebo: suggestion for application to long-term weight-control drug development. *Drug Des Dev and Therapy*, 09 Sep 2015, 9:5185-5194

[22] Antman MD, Gudmundsson OS. Case Study: Valacyclovir: A Prodrug of Acyclovir. *Prodrugs* 2007 pp 1369-1376

[23] Zhong Q, Zhang C, Zhang Q et al. Boronic prodrug of 4-hydroxytamoxifen is more efficacious than tamoxifen with enhanced bioavailability independent of CYP2D6 status. *BMC Cancer*. 2015 Sep 9;15:625. PMCID: PMC4563833.

[24] Ehrnebo, M., Nilsson, SO. & Boréus, L.O. Pharmacokinetics of ampicillin and its prodrugs bacampicillin and pivampicillin in man. 1979 *J of PK and Biopharm* **7,** 429–451

[25] Shin JM, Kim N. Pharmacokinetics and pharmacodynamics of the proton pump inhibitors. *J Neurogastroenterol Motil*. 2013;19(1):25-35. doi:10.5056/jnm.2013.19.1.25

[26] Pal A, Banik PA. Highly Efficient Prodrugs: Design and Therapeutic Applications. *Orient J of Pure and Appl Chem* 2020 Volume 36, Number 6

[27] Frey BM, Frey FJ. Clinical Pharmacokinetics of Prednisone and Prednisolone. *Clinical Pharmacokinetics* 1990 19, 126–146

[28] Dean L, Kane M. Mercaptopurine Therapy and TPMT and NUDT15 Genotype. 2012 Sep 20 [Updated 2020 Oct 26]. In: Pratt VM, Scott SA, Pirmohamed M, et al. Medical Genetics Summaries: National Center for Biotechnology Information

[29] Vickers S, Duncan CA, Chen IW et al. Metabolic disposition studies on simvastatin, a cholesterol-lowering prodrug. *Drug Metab Dispos*. 1990 Mar-Apr;18(2):138-45. PMID: 1971563

47. Further evidence is the fact that many known homeopathic compounds naturally exist in the prodrug form. These include: Romidepsin[30], Butyrin[31], Psilocybin[32], Salvestrols[33] (which are prodrugs for resvetrol) Spiruchostatins[34], Prontosil[35], Hydroxybutyric acid (GHB)[36], Melatonin[37], Phytoestrogens[38], Baicalin[39], Matricin[40], Sennoside A[41], Glycyrrhizin[42], Barbaloin[43],

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[30] Bronson J, Dhar M, Ewing W et al. Chapter 26 - 2010. *Ann rep in med chem* Volume 46, 2011, Pages 433-502

[31] MengLia B, van Eschab, G, Wagenaar TM et al. Pro- and anti-inflammatory effects of short chain fatty acids on immune and endothelial cells *Eur J of Pharmacol* Volume 831, 15 July 2018, Pages 52-59

[32] Ricardo Jorge Dinis-Oliveira (2017) Metabolism of psilocybin and psilocin: clinical and forensic toxicological relevance, Drug Metabolism Reviews, 49:1, 84-91

[33] The Role of Salvestrols in the Prevention and Treatment of Cancer Article in Integrative Cancer Therapies, March 2009 Copyright (C) Orthokennis https://www.orthokennis.nl/artikelen/the-role-of-salvestrols-in-the-prevention-and-treatment-of-cancer

[34] Wang C, Wesener SR, Zhang H etal. An FAD-Dependent Pyridine Nucleotide-Disulfide Oxidoreductase Is Involved in Disulfide Bond Formation in FK228 Anticancer Depsipeptide. *Chem & Biol* Volume 16, Issue 6, 26 June 2009, Pages 585-593

[35] Silverman RB, Holladay MW. Prodrugs and Delivery Systems in The Organic Chemistry of Drug Design and Drug Action (Third Edition), 2014

[36] Busardò FP, Gottardi M, Tini A, Minutillo A, Sirignano A, Marinelli E, Zaami S. Replacing GHB with GBL in Recreational Settings: A New Trend in Chemsex. *Curr Drug Metab*. 2018;19(13):1080-1085

[37] Thoại PV, Nguyen HN. Design and Synthesis of Sustain-Acting Melatonin Prodrugs *J of Chem*, vol. 2013, Article ID 684760, 6 pages, 2013

[38] Arroo, R.R.J., Beresford, K., Bhambra, A.S. et al. Phytoestrogens as natural prodrugs in cancer prevention: towards a mechanistic model. 2014 *Phytochem Rev* 13, 853–866

[39] Meritxell Teixido. Baicalin, a prodrug able to reach the CNS, is a prolyl oligopeptidase inhibitor 2008, *Bioorganic & Medicinal Chemistry* 16 (2008) 7516–7524

[40] Dubey A, Dotolo S, Ramteke PW, Facchiano A, Marabotti A. Searching for Chymase Inhibitors among Chamomile Compounds Using a Computational-Based Approach. *Biomolecules*. 2018;9(1):5

[41] Takayama K, Tabuchi N, Fukunaga M, Okamura N. Rhein 8-O-β-D-Glucopyranoside Elicited the Purgative Action of Daiokanzoto (Da-Huang-Gan-Cao-Tang), Despite Dysbiosis by Ampicillin. *Biol Pharm Bull*. 2016;39(3):378-83

[42] Shim SB, Kim NJ, Kim DH. Beta-glucuronidase inhibitory activity and hepatoprotective effect of 18 beta-glycyrrhetinic acid from the rhizomes of Glycyrrhiza uralensis. *Planta Med*. 2000 Feb;66(1):40-3

[43] Patela DK, Patel K, Tahilyani V. Barbaloin: A concise report of its pharmacological and analytical aspects *Asian Pacific Journal of Tropical Biomedicine* Volume 2, Issue 10, October 2012, Pages 835-838

Geniposide[44], Paeoniflorin[45], Lignans[46], Lovastatin[47], Progabide[48], Salicin[49] and Psammaplin[50] Likewise, the possibility exists that the metabolized components of Prevagen can be activated into pharmacologically active moieties, meeting the definition of a prodrug. Dr. Berg fails to consider this possibility.

V. PRODRUGS AND LARGE MOLECULE PHARMACOLOGY

48. Since the late 1980s, high throughput screening and computer modeling have been used to theoretically model and predict compound/receptor activity and activity of small-molecule pharmacology.[51] Specialists in the discipline of theoretical chemistry have predicted that using this type of modeling has led to most or all permutations of low molecular weight compounds having already been screened for drug/receptor activity as potential therapeutic pharmacologics

[44] Y.C. Hou, S.Y. Tsai, P.Y. Lai, Y.S. Chen, P.D.L. Chao. Metabolism and pharmacokinetics of genipin and geniposide in rats. *Food and Chemical Toxicology*, 2008 Volume 46, Issue 8 Pages 2764-2769

[45] Kimura I, Nojima H, Kimura M. Analysis of Chemical-Structure-Activity Relationships to Identify New Pro-Drugs with Unique Mechanisms of Actions in Kampo Medicines and Other Natural Products, *Studies in Natl Prod Chem*. Volume 24, Part E, 2000, Pages 875-932

[46] Pilkington LI. Lignans: A Chemometric Analysis. *Molecules* 2018, 23, 1666; doi:10.3390/molecules23071666

[47] Alberts AW, MacDonald JS, Till AE et al. Lovastatin. *Cardiovascular Drug Reviews* 1989 Vol. 7, No. 2, pp. 89- 109

[48] Farraj, N.F., Davis, S.S., Parr, G.D. et al. The Stability and Solubility of Progabide and Its Related Metabolic Derivatives. *Pharm Res* 1988 5, 226–231

[49] Akao T, Yoshino T, Kobashi K, Hattori M. Evaluation of salicin as an antipyretic prodrug that does not cause gastric injury. *Planta Med*. 2002 Aug;68(8):714-8

[50] Kim DH, Shin J, Kwon HJ. Psammaplin A is a natural prodrug that inhibits class I histone deacetylase. *Exp & molec med* 2007-3-6

[51] Richards WG. Theoretical chemistry in drug discovery. *Eur J Med Chem* (1994) 29,499-502

for known therapeutic targets.[52] [53] For this reason, novel engineering of molecules for new drugs are needed in the form of larger molecular-weight compounds and/or prodrugs.[54] Many new small-molecule drugs that have been approved in the past decade are those for rare diseases.[55] [56] [57] Case in point, in 2008, approximately one-third of the drugs approved by the FDA were prodrugs.[58]

49. Both naturally found and prospectively designed prodrugs may be larger molecules which have the ability to have better absorption, improved delivery or superior efficacy. They exist in an inactive form, and following an enzymatic or other chemical process are designed to break down inside the body into an active form. Other reasons for this type of formulation either by design or by mother nature, are many and include the fact that the compound may be more stable during manufacture or storage as the prodrug form, or because the prodrug has superior potency, efficacy, safety, pharmacokinetics, or other favorable pharmacology.

50. Activation of a prodrug from active to an inactive form may occur *in almost any part of the body*, as well as intracellularly or extracellularly. A peer-reviewed article published by

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[52] Huy NT, Chi PL, Nagai J et al. High-Throughput Screening and Prediction Model Building for Novel Hemozoin Inhibitors Using Physicochemical Properties. *Antimicrob Agents Chemother*. 2017 Jan 24;61(2):e01607-16

[53] Talluri S. Molecular Docking and Virtual Screening based prediction of drugs for COVID-19 *Combinatorial Chemistry & High Throughput Screening* (2020) 23: 1.

[54] Morrow T. Defining the difference: What Makes Biologics Unique. *Biotechnol Healthc*. 2004 Sep; 1(4): 24-26,28-29

[55] 2018 FDA approvals. https://www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products/novel-drug-approvals-**2018**

[56] 2019 FDA approvals. https://www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products/novel-drug-approvals-**2019**

[57] 2020 FDA approvals. https://www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products/novel-drug-approvals-**2020**

[58] Huttunen KM, Raunio H, Rautio J. Prodrugs – from serendipity to rational design. *Pharmacol Rev* 2011, 63, 750–771

the FDA's pharmacologist at the Center for Drug Evaluation and Research (CDER) even specifies that this could include enzymatic processes at the level of the gut and/or at the level of gastrointestinal fluids.[59] [60]

Tissue or location of prodrug conversion:	**Drug examples:**
Metabolic Tissues (GI, mucosal cell, lung, etc.)	Cabamazepine, Captopril, Carisoprodol, Heroin, Molsidomine, Paliperidone, Phenacetin, Primidone, Psilocybin, Suldinac Tetrahydrofurfuryl disulfide
Therapeutic Target Tissues/Cells	Acyclovir, 5-Flurouracil, Cyclophosphamide, Diethlstilbestrol diphosphate, L-Dopa, 6-Mercaptopurine, Mitomycine C, Zidovudine
GI Fluids	Lisdexamfetamine, Loperamide oxide, Oxyphenisatin, Sulfasalazine
Systemic Circulation and Other Extracellular Fluid Compartments	Acetylsalicylate, Bacampicillin, Bambuterol, Chloramphenicol succinate, Dihydropyridine, pralixoxime, Dipivefrin, Fosphenytoin

VI. PHARMACOGENETICS/PHARMACOGENOMICS

51. Genetic variations in human beings may lead to variations in response to food, drugs, or dietary supplements. Human beings are more than 99.9% (or more) the same, however

[59] Wu KM. A New Classification of Prodrugs: Regulatory Perspectives. *Pharmaceuticals (Basel)*. 2009;2(3):77-81. Published 2009 Oct 14. doi:10.3390/ph2030077

[60] Zawliska JB, Wojcieszak J, Olejniczak AB. Prodrugs: A challenge for the drug development *Pharmacological Reports* 2013, 65, 1–14

the remaining percentage is what sometimes makes a pharmacists and pharmacologist's job very unpredictable and complicated. Pharmacogenetics / Pharmacogenomics (used interchangeably) have been defined as the study of variability in response due to one's specific individual genetic disposition.[61]

52. The documented history of pharmacogenetics can be traced as far back as 510 BCE when Pythagoras reported his observations which noted that some, but not all, individuals who ingested fava beans could suffer a significant or potentially fatal adverse reaction.[62] Pharmacogenetics has so many implications and is so vast and evolving, that many new, academic peer-reviewed journals have emerged over the past two decades to address the subject. These periodicals include, but are not limited to:

- *Pharmacogenomics,*
- *The American Journal of Pharmacogenomics,*
- *The Pharmacogenomics Journal,*
- *International Society of Pharmacogenomics, pharmacogenetics and genomics,*
- *Pharmacogenetics and pharmacogenomics,*
- *The Journal of Pharmacogenomics & Pharmacoproteomics,*
- *Pharmacogenomics research,*
- *Current Pharmacogenomics and Personalized Medicine and*
- *The Pharmacogenomics Journal*

[61] Nebert DW. Pharmacogenetics and pharmacogenomics: why is this relevant? *Clin Genet*. 1999;56:345–347
[62] Nebert DW. Pharmacogenetics and pharmacogenomics: why is this relevant? *Clin Genet*. 1999;56:345–347

This list is non-exhaustive and does not mention the *hundreds* of other pharmacology, pharmacy, medicine and basic science publications and journals which may also publish original topics or reviews addressing topics in pharmacogenomics, et cetera.

53. This is because pharmacogenomics is viewed as an emerging and critical specialty of its own, and an obviously highly important area for improving drug therapy and prescribing in the future. These publications have led to the FDA recognizing that over 100 different variations in prescription drug dosing[63] for which published pharmacogenomic data support therapeutic management associations as well as variations in metabolism and drug response.

54. The manner in which different individuals metabolize food or drugs can occur due to inborn errors of metabolism, or just simple variation within the human genome which is seen about every 500–1000 bases[64] or as single nucleotide polymorphisms.[65] Dr. Berg's report illustrates a perceptibly outdated, and in my opinion, a non-pharmacologist's, non-FDA regulatory level of consideration regarding absorption, distribution, metabolism and excretion. His approach and analysis appears to follow "a one hypothesis fits all" meaning whereby only one modeling methodology will or will not work the same way on everyone. In my opinion, this ignores accepted pharmacogenomic concepts. He does not consider proven scientific and clinical factors, well-documented in the form of thousands of reviews, articles, publications, textbooks, and official FTC guidance documents -- not to mention lay press articles -- written over the past several decades.

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[63] Pharmacogenetic Associations for which the Data Support Therapeutic Management Recommendations for PK or safety. Accessed at: https://www.fda.gov/medical-devices/precision-medicine/table-pharmacogenetic-associations

[64] Roses AD. Pharmacogenetics and the practice of medicine. *Nature.* 2000 Jun 15; 405(6788):857-65

[65] Gray IC, Campbell DA, Spurr NK. Single nucleotide polymorphisms as tools in human genetics. *Hum Mol Genet.* 2000 Oct; 9(16):2403-8

VII. ASPIRIN RESISTANCE -- WHY EVERY DRUG OR SUPPLEMENT DOESN'T ALWAYS WORK ON EVERY SINGLE PATIENT

55. It has been estimated that approximately one-third of adults have what is referred to as "aspirin resistance." In these individuals, aspirin's antiplatelet effect is lower than what is needed for the clinical outcome of cardioprotective anticoagulation. Little consistency exists about which methodology should be implemented to identify patients who show resistance to aspirin, and the definite possibility exists that genetic variations in metabolism could be responsible.[66] [67] [68] [69] [70] [71]

56. The major controversy relating to aspirin therapy is why particular patients do not benefit from such therapy and how they might be identified. It has been suggested that some patients require a higher dose of aspirin than is normally recommended to achieve the expected antiplatelet effect. It is unclear whether these patients: 1) simply receive too low an aspirin dose;

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[66] Kuliczkowski W, Halawa B, Korolko B et al. Aspirin resistance in ischemic heart disease. *Kardiol Pol* 2005;62:14-9

[67] Angiolillo DJ, Fernandez-Ortiz A, Bernardo E et al. Influence of aspirin resistance on platelet function profiles in patients on long-term aspirin and clopidogrel after percutaneous coronary intervention. *Am J Cardiol* 2006;97:38-43

[68] Hegason CM, Bolin KM, Hoff JA et al. Development of aspirin resistance in persons with previous ischemic stroke. *Stroke* 1994;25:2331-6

[69] Kawasaki T, Ozeki Y, Igawa T, Kambayashi J-I. Increased platelet sensitivity to collagen in individuals resistant to low-dose aspirin. *Stroke* 2000;31:591-6

[70] Macchi L, Christianes L, Brabant S, Sorel N, Allal J, Mauco, et al. Resistance to aspirin is associated with platelet sensitivity to adenosine diphosphate. *Thromb Res* 2002;107:45-9

[71] Zimmerman N, Wenk A, Kim U, et al. Functional and biochemical evaluation of platelet aspirin resistance after coronary artery bypass surgery. *Circulation* 2003;108:542-7

2) are not compliant; 3) have differing abilities to absorb aspirin; or 4) have an underlying genetic disposition that renders aspirin ineffective.[72] [73] [74] [75] [76] [77]

57. Likewise, the clinical results from the use of Prevagen can vary and may not work in all individuals for the same reasons that aspirin, and other drugs or dietary supplements, do not. These include, but are not limited to: dose, compliance, resistance, pharmacogenomics, metabolism and/or genetic polymoprhisms. The bottom line is: studies have shown positive response from the use of Prevagen.

VIII. MOLECULE SIZE

58. In his report, Dr. Berg notes "*Proteins, in contrast, generally cannot survive digestion in the stomach intact*" and cites the larger size of Prevagen as a factor for its rapid deterioration in the stomach. (Berg ¶¶ 17-18.) However, because he is not a pharmacologist or because his understanding of metabolism may not be complete, Dr. Berg fails to consider the fact that it may be possible for proteins and biologics *even larger* than Prevagen to survive the gastric conditions of the stomach. In contrast to that, clinical research has shown us that many larger,

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[72] Patrono C, García Rodríguez LA, Landolfi R, Baigent C. Low-dose aspirin for the prevention of atherothrombosis. *N Engl J Med* 2005;353:2373-83

[73] Buchanan MR. Biological basis and clinical implications of acetylsalicylic acid resistance. *Can J Cardiol* 2006;22:149-51

[74] Eikelboon JW, Hirsh J, Weitz JI et al. Aspirin-resistant thromboxane biosynthesis and risk of myocardial infarction, stroke, or cardiovascular death in patients at high risk for cardiovascular events. *Circulation* 2002;105:1650-5

[75] Patrono C. Aspirin resistance: definition, mechanisms and clinical read-outs. *J Thromb Haemost* 2003;1:1710-3

[76] Hennekens CH, Schor K, Weisman S, Fitzgerald GA. Semantic complexity and aspirin resistance. *Circulation* 2004;110:1706-8

[77] Cattaneo M. Aspirin and clopidogrel: efficacy, safety, and the issue of drug resistance. *Aterioscler Throm Vasc Biol* 2004;24:1980-7

complex things -- including complex biological organisms -- have the potential to survive the enzymatic and chemical conditions in the human stomach.

59. Dr. Berg's certitudes about the destruction of any 'large protein structure' within the gut is reminiscent of the clinical conflicts that delayed the identification of Helicobacter pylori ("H. Pylori") by Drs. Barry Marshall and J. Robert Warren in 1983. For nearly a century prior, it was incorrectly assumed that the extremely low pH conditions in the stomach made the stomach a "*sterile*" environment where it was impossible for anything to survive, and that the stomach enzymatically or chemically broke down and/or otherwise inactivated anything that came within its contact. This incorrect consensus parroted widely among clinicians was that any medical cases involving stomach inflammation and ulceration had to be an acid-related or psychosomatic condition.[78]

60. Both of these Nobel-winning scientists were questioned by colleagues and peers around the world until they were irrefutably able to prove their findings, with objective laboratory data. Both scientists later were awarded the Nobel Prize for Medicine.[79]

61. In addition to H. Pylori, anyone who has suffered from food-borne illness A/K/A/ "food poisoning" from improperly prepared foods can attest to the same. In truth, even large microorganisms that are not digested in the stomach can actually survive and thrive in the stomach. Examples include but are not limited to:

[78] Dunn BE, Phadnis SH. Structure, function and localization of Helicobacter pylori urease. *Yale J Biol Med*. 1998 Mar-Apr;71(2):63-73

[79] Pincock S. Nobel Prize winners Robin Warren and Barry Marshall. *Lancet* Vol 366 October 22, 2005

- **Escherichia Coli** ("E. Coli") from ground beef or improperly washed fresh produce. E. coli affect about 300,000 per year in the USA alone.

- **Listeria monocytogenes** from any food that comes into contact with animal feces such as cheese or deli meats. There are about 1,600 cases of listeria per year in the USA alone.

- **Salmonella** from raw fruits, vegetables and meats. Salmonella affects about 1.35 million people per year in the USA alone.

- **Campylobacter** from infected poultry, shellfish or contaminated water. Campylobacter affects about 1.3 million people per year in the USA alone.

- **Clostridium difficile** ("C. diff") is typically a nosocomial-acquired infection that can be life threatening. Clostridium difficile affects about half a million people per year in the USA alone.

62. There is increasing discussion of *Dientamoeba fragilis*, *Giardia*, *Shigella* spp, *Aeromonas* spp., *Plesiomonas* spp., and newly recognized pathogens (*Acrobacter, Larobacter,* enterotoxigenic *Bacteroides fragilis*) as potential causes of infection as well. There are many viral sources of gastrointestinal causes of infectious diseases including classes of the norovirus, rotavirus, and astrovirus. Dr. Berg's blanket assertion that Prevagen's active ingredient cannot survive digestion due to its size, and could never have pharmacological activity in the body merely because of its size, without providing objective scientific data to support this conclusion, is contrary to well-founded pharmacological and other scientific concepts.

IX. ACTIVE TRANSPORT OF PREVAGEN IN THE GUT AND BLOOD-BRAIN BARRIER

63. Dr. Berg is also in disagreement with specific findings on the well-established cellular biology concept of active transport. Active transport is the body's ability to employ energy to forcibly move molecules across a cell membrane from a region of lower concentration to a region of higher concentration, against a concentration gradient.

64. Published data has shown that the dietary intake of apoaequorin together with dietary cholesterol has the potential to "*greatly facilitate*" the uptake of intact protein from the gut.[80]

65. Published, peer-reviewed modeling studies indicate that the presence of a CARC or CRAC motif in a protein usually indicates its intrinsic capability to interact with cholesterol.[81] Of note, Prevagen contains at least four of these separate and distinct cholesterol-binding sites to bind cholesterol which can assist with active transport into the blood stream or into the brain.[82] [83]

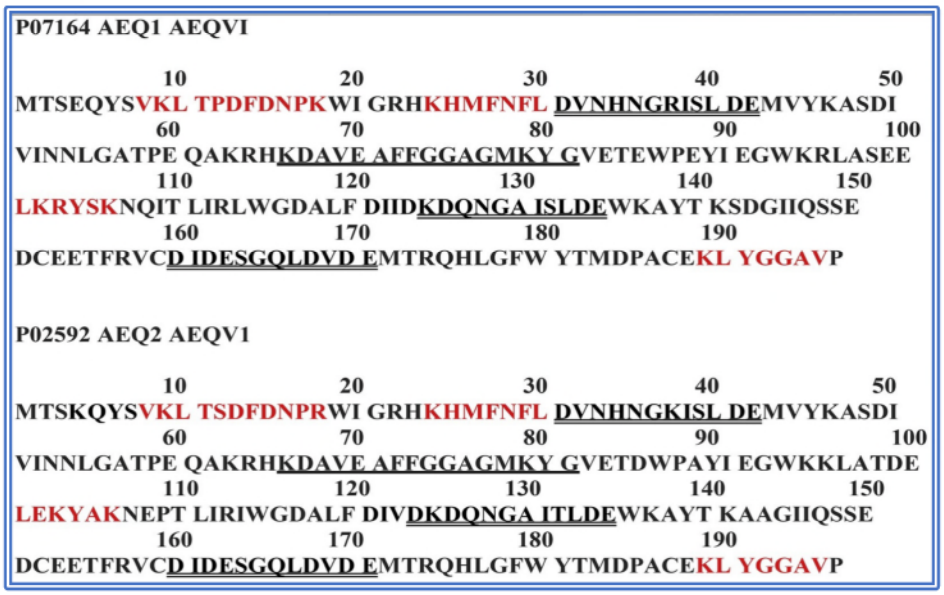
[80] Morrill GA, Kostellow AB, Gupta RK. Computational comparison of a calcium-dependent jellyfish protein (apoaequorin) and calmodulin-cholesterol in short-term memory maintenance. *Neuroscience Letters* Volume 642, 6 March 2017, Pages 113-118

[81] J. Fantini, C. Di Scala, L.S. Evans, et al. A mirror code for protein-cholesterol interactions in the two leaflets of biological membranes *Scientific reports, nature.com*., 6 (2016), p. 21,907

[82] Morrill GA, Kostellow AB, Gupta RK. Computational comparison of a calcium-dependent jellyfish protein (apoaequorin) and calmodulin-cholesterol in short-term memory maintenance. *Neuroscience Letters* Volume 642, 6 March 2017, Pages 113-118

[83] Murata M, Peranen J, Schreiner R. VIP21/caveolin is a cholesterol-binding protein. *Proc. Natl. Acad. Sci*., 92 (1995), pp. 10339-10343

Figure 1: Protein Domain Sequence of Prevagen



In Figure 1 above, a comparison of the protein domains/motifs and Ca+ -binding sites of the two isoforms of apoaequorin (top: P07164 and bottom: P02592). The cholesterol-binding (CRAC/CARC) which assist with active transport from the GI into the bloodstream and the bloodstream into the brain domains are **highlighted in red (n=4).** The calcium binding sites which cause pharmacological activity inside the brain are **double underlined (n=3).**

66. The apoaequorin/cholesterol and calmodulin/cholesterol complex could avoid proteolysis and cross the blood-brain barrier and therefore be more effective as a dietary supplement, and this could occur naturally at the level of the gut, if ingestion of Prevagen occurred with cholesterol-containing foods or in patients that are genetically hypercholesterolemic subsets of the population. Cholesterol binds to the lysine (K) and arginine (R) amino acids in the

cholesterol-binding CRAC/CARC motif and would presumably block sites of serine protease cleavage[84] and facilitate uptake across the blood-brain barrier.

67. Although the mechanism of action of Prevagen is unknown, published findings state that cholesterol binding may facilitate Prevagen uptake across the blood-brain barrier and/or entry into cells of the hippocampus where it is known to elicit a clinical effect through its effect on calcium signaling. That further suggests that the apoaequorin/cholesterol complex may be taken up by hippocampal neurons and serve to facilitate memory consolidation.[85]

68. Stated more simply, any dietary or circulating cholesterol could assist in actively transporting Prevagen through both the gut and into the brain. It is possible that either of these pathways relating to the mechanism of action is worth exploring, but Dr. Berg's categorical assertion that Prevagen cannot work is unsupported by the weight of the scientific evidence. In my opinion, not using objective scientific findings to make an assertion is certainly contrary to the manner in which science progresses. At a minimum, these published findings detail yet another proof of concept of the pharmacology of Prevagen.

X. FUNDAMENTAL CONCEPTS OF CALCIUM SIGNALING AND MEMORY

69. In humans, age-related memory impairments begin in mid-life and cognitive weakening continues with advancing age. An important aspect of defining memory decline is the distinction between dementia as a result of neurological diseases, such as Alzheimer's disease, and memory loss not specifically associated with disease. Within the population of elderly without

[84] Rawlings ND, Barrett AJ. Families of serine peptidases. *Meth. Enzymol.*, 244 (1994), pp. 19-61

[85] Morrill GA, Kostellow AB, Gupta RK. Computational comparison of a calcium-dependent jellyfish protein (apoaequorin) and calmodulin-cholesterol in short-term memory maintenance. *Neuroscience Letters* Volume 642, 6 March 2017, Pages 113-118

dementia, there is considerable variability in memory. This variability is likely to be a result of the interaction of genetic make-up and environment, which influences several processes for cell maintenance and repair including oxidative damage and cholesterol metabolism, leading to disruption of calcium homeostasis, and ultimately calcium-dependent processes that underlie memory. The role of calcium in neurological modalities is widely recognized.[86]

70. Within the population of healthy individuals, a slight, though statistically significant, decrease in memory function is observed as people aged from 20 to 50 years, and a more rapid rate of decline, specific for episodic memory, is observed in individuals aged >50 years.[87] [88] [89] [90] [91] Memory deficits are not an inevitable consequence of aging. While the proportion of individuals with memory problems increases with age, some individuals maintain normal cognitive function throughout life.

71. Memory loss in normal aging appears to be progressive, and treatments designed to prevent cognitive decline would appear to be advantageous. The obvious treatment strategy is to identify individuals at risk for memory deficits and treat age-related changes in biological processes before any easily, visually measurable changes in the CNS begin. Since calcium

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[86] Hendler S, Rorvik D. "Calcium" In: PDR for Nutritional Supplements. Thomson Healthcare, Montvale, NJ, (2001) pp. 74-79

[87] Larrabee GJ, Crook III TH. Estimated prevalence of age-associated memory impairment derived from standardized tests of memory function. *Int Psychogeriatr* 1994; 6 (1): 95-104

[88] Verhaeghen P, Salthouse TA. Meta-analyses of age-cognition relations in adulthood: estimates of linear and nonlinear age effects and structural models. *Psychol Bulletin* 1997; 122 (3): 231-49

[89] Park DC, Lautenschlager G, Hedden T, et al. Models of visuo-spatial and verbal memory across the adult life span. *Psychol Aging* 2002; 17 (2): 299-320

[90] Zelinski EM, Gilewski MJ, Schaie KW. Individual differences in cross-sectional and 3-year longitudinal memory performance across the adult life span. *Psychol Aging* 1993; 8 (2): 176-86

[91] Small SA, Stern Y, Tang M, et al. Selective decline in memory function among healthy elderly. *Neurology* 1999; 52 (7): 1392-6

homeostasis dysfunction far precedes any visible changes in brain volume, and calcium has a clearly established role throughout the literature, it seems only reasonable to attempt to engineer a neuronal calcium-modulating drug to affect downstream cell maintenance and repair.

72. Alzheimer's disease is the leading cause of cognitive loss and neurodegeneration in the developed world.[92] It is also the most common cause of dementia in the elderly. With the lack of a cure, and only mildly effective symptomatic treatments at best, there is a great impetus to better treat this as of yet incurable dementia. Dyshomeostasis of calcium is evident in the AD brain.[93] Neuronal aging is specifically associated with the alteration of increased neuronal calcium, leading to old neurons being more vulnerable.[94] [95] In particular, calcium dyshomeostasis has been reported in both peripheral neurons and the brain during the aging process.[96] [97] [98]

73. Neurons depend on highly specific calcium signaling systems[99] responsible for regulating neural functions such as brain rhythms, information processing, learning and memory. Remodeling of these calcium signaling pathways that create inappropriate calcium responses have

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[92] McBride SMJ, Choi CH, Schoenfeld BP etal. Pharmacological and Genetic Reversal of Age-Dependent Cognitive Deficits Attributable to Decreased presenilin Function *J Neurosci*. Jul 14, 2010; 30(28): 9510–9522

[93] Canzoniero, L. M. & Snider, B. J. Calcium in Alzheimer's disease pathogenesis: too much, too little or in the wrong place? *J Alzheimers Dis* 2005; 8(147–154), 209–115

[94] Verkhratsky A.; Toescu EC. Calcium and neuronal ageing. *Trends Neurosci*. 1998, 21, 2–7

[95] Toescu EC, Verkhratsky A, Landfield PW. Ca2+ regulation and gene expression in normal brain aging. *Trends Neurosci.* 2004, 27, 614–620

[96] Toescu EC, Verkhratsky A. The importance of being subtle: Small changes in calcium homeostasis control the cognitive decline in normal aging. *Aging Cell* 2007, 6, 267–273

[97] Foster TC. Calcium homeostasis and modulation of synaptic plasticity in the aged brain. *Aging Cell* 2007, 6, 319–325

[98] Bezprozvanny, I. Calcium signaling and neurodegenerative diseases. *Trends Mol. Med*. 2009, 15, 89–100

[99] Berridge MJ. Neural calcium signaling. *Neuron*. 2012;21:13–26

been linked to many major neural diseases[100] [101] [102] [103] [104] [105] [106] [107] In the case of Alzheimer's disease, calcium levels are set too high and this has a negative impact on many neural functions and particularly memory formation and consolidation.

74. Alzheimer's disease has a well-known prodromal stage when symptoms beginslowly, and may or not be immediately evident to most people.[108] This provides a therapeutic window when pathological processes are still responsive to treatment. Alzheimer's disease begins with a decline in cognition followed by neuronal cell death and dementia. These changes have been linked to a deregulation of calcium signaling caused by a progressive increase in the resting level of calcium. Several studies have even shown that the up-regulating of calcium homeostasis occurs well before any symptoms of memory dysfunction, detailing that calcium increase is a predictor event of AD.[109] The earlier hypotheses related to the cause of Alzheimer's disease was

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[100] Khachaturian ZS. Calcium, membranes, aging, and Alzheimer's disease. Introduction and overview. *Ann NY Acad Sci.* 2013;568:1–4

[101] LaFerla FM. Calcium dyshomeostasis and intracellular signaling in Alzheimer's disease. *Nat Rev Neurosci*. 1989;3:862–872

[102] Stutzmann GE. The pathogenesis of Alzheimer's disease is it a lifelong 'calciumopathy'. *Neuroscientist*. 2005;13:546–559

[103] Thibault O, Gant JC, Landfield PW. Expansion of the calcium hypothesis of brain ageing and Alzheimer's disease: minding the store. *Aging Cell*. 1992;6:307–317

[104] Bezprozvanny I, Mattson MP. Neuronal calcium mishandling and the pathogenesis of Alzheimer's disease. Trends Neurosci. 2012a;31:454–463

[105] Berridge MJ. Calcium signaling and Alzheimer's disease. *Neurochem Res*. 1998;36:1149–1156

[106] Berridge MJ. Calcium signaling remodeling and disease. *Biochem Soc Trans*. 2010;40:297–309

[107] Berridge MJ. Dysregulation of neural calcium signaling in Alzheimer disease, bipolar disorder and schizophrenia. *Prion*. 2011;6:1–12

[108] Jack CR. Jr. Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. *Lancet Neurol* 2013 12, 207–216

[109] Etcheberrigaray R, Hirashima, N, Nee L, et al. Calcium responses in fibroblasts from asymptomatic members of Alzheimer's disease families. *Neurobiol. Dis*. 1998, 5, 37–45

that accumulation of amyloid plaque was the cause of the disease, much like atherosclerotic plaque in the heart was the cause of heart disease. Current thinking more specifically links increased cytosolic calcium levels that, in turn, promote amyloid ß plaque production levels, and its subsequent cognitive/memory neurotoxicity, while the accumulation of amyloid ß plaques results in a feedback loop that results in increased neural calcium signaling.[110] Calcium has been shown to play a role in promoting the formation of amyloid ß plaque production in the brain, reducing blood flow to the brain and leading to atrophy.[111] [112] In other words, there is a synergistic disease mechanism between calcium and amyloid ß that could self-propagate each other and intensify neurodegeneration in Alzheimer's disease patients and other patients with memory and cognitive defects.[113]

75. Calcium is a very important signaling ion. Elsevier, which is a publisher that oversees over 2,500 periodicals alone, has entire peer reviewed journals strictly dedicated to calcium as a signaling modality.[114] Separate from this journal, the approximately 100 unique experiments cited here have empirically and specifically shown that alterations in calcium homeostasis underlie the reduced cellular function characteristic of the normal aging process of

[110] Pchitskaya E, Popugaeva E, Bezprozvanny I. Calcium signaling and molecular mechanisms underlying neurodegenerative diseases. *Cell Calcium* 2018, 70, 87–94

[111] Querfurth HW, Selkoe DJ. Calcium ionophore increases amyloid (beta) peptide production by cultured cells. *Biochemistry* 1994, 33, 4550–4561

[112] Bezprozvanny I, Mattson MP. Neuronal calcium mishandling and the pathogenesis of Alzheimer's disease. *Trends Neurosci*. 2008, 31, 454–463

[113] Demuro A, Mina E, Kayed, R etal. Calcium dysregulation and membrane disruption as a ubiquitous neurotoxic mechanism of soluble amyloid oligomers. *J. Biol. Chem*. 2005, 280, 17294–17300

[114] https://www.journals.elsevier.com/cell-calcium/

the brain.[115] [116] [117] [118] [119] [120] Calcium-binding compounds (for example, Prevagen) have been prominently recognized as protective factors in neuronal populations susceptible to toxicity via calcium and calcium-mediated events.[121] [122] [123] [124] [125] [126] [127]

XI. MEMORY PHYSIOLOGY

76. When animals learn hippocampus-dependent associative and spatial tasks, hippocampal neurons become more excitable as a result of reductions in the post-burst, slow afterhyperpolarization. The calcium-activated potassium current that mediates this

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[115] Foster TC, Norris CM. Age-associated changes in Ca+ -dependent processes: relation to hippocampal synaptic plasticity. *Hippocampus* 1997 7, 602-612

[116] Kelly KM, Nadon NL, Morrison JH, et al. The neurobiology of aging. *Epilepsy Res*. 2006 68 (Suppl. 1), S5-S20

[117] Squier TC, Bigelow, DJ. Protein oxidation and age-dependent alterations in calcium homeostasis. *Front. Bio* 2000 5, D504-26

[118] Thibault 0, Gant JC, Landfield, PW. Expansion of the calcium hypothesis of brain aging and Alzheimer 's disease: minding the store. *Aging Cell* 2007; 6 (3), 307-317

[119] Toescu EC, Vreugdenhil , M. Calcium and normal brain aging. *Cell Calcium* 2010 :47;2 158-164

[120] Verkhratsky A, Toescu EC. Calcium and neuronal ageing. *Trends Neurosci* 1998 21:1, 2-7

[121] Alpar A, Attem SJ, Mulder J etal. The renaissance of Ca2+-binding protein s in the nervous system: secretagogin takes center stage. *Cell Signal* 2012; 24 (2). 378-387

[122] Iacopino AM, Christakos S. Specific reduction of calcium-binding protein (28-kilodalton calbindin-D) gene expression in aging and neuro-degenerative diseases. *Proc. Natl. Acad. Sci.* USA 1990 87, 4078-4082

[123] Foster TC, Sharrow KM, Masse JR et al. Calcineurin links Ca2+ dysregulation with brain aging. *J Neurosci*. 2001 21 (11), 4066-40 73

[124] Kumar A, Bodhinathan K, Foster TC. Susceptibility to calcium dysregulation during brain aging. *Front. Aging Neurosci*. 2009 27 (1), 2

[125] Matteson MP, Chan SL, Duan W. Modification of brain aging and neurodegenerative disorders by genes, diet , and behavior. *Physiol. Rev*. 2002 82,637-672

[126] Rogers J, Khan M, Ellis J. Calretinin and other CaBPs in the nervous system. *Adv. Exp. Med. Biol*. 1990 269, 195-203

[127] Heizmann CW, Braun K. Changes in calcium-binding proteins in human degenerative disorders. *Trends Neurosci*. 1992 15, 259-264

afterhyperpolarization is activated by the calcium influx that occurs when a series of action potentials fire and serves as a modulator of neuronal firing frequency. Neuronal calcium buffering processes change and/or voltage-dependent calcium currents increase during aging, thereby leading to enhancements in the slow afterhyperpolarization, increased spike frequency accommodation and age-associated impairments in learning.

77. Neuronal nuclear calcium controls the transcription of genes that also play a role in the structural changes that are responsible for the formation of long-term memory. The calcium signaling pathway is integral to memory consolidation. This signaling, which is moderated by the calmodulin protein, is regulated by the presence of calcium ions.[128] The hippocampus is critical for the formation of new memories about experienced events.[129] [130] Memory consolidation is a category of processes that stabilize a memory trace after its initial acquisition.[131] Consolidation is distinguished by two specific processes, synaptic consolidation, which is synonymous with late-phase long-term potentiation[132] occurring within the first few hours after learning, and systems

[128] Limbäck-Stokin K, Korzus E, Nagaoka-Yasuda R et al. Nuclear Calcium/Calmodulin Regulates Memory Consolidation *J Neuroscience* Dec 2004, 24 (48) 10858-10867

[129] Eichenbaum H. Hippocampus: cognitive processes and neural representations that underlie declarative memory *Neuron*, 44 (2004), pp. 109-120

[130] S.B. Duss SB, Reber TP, Hanggi J etal. Unconscious relational encoding depends on the hippocampus *Brain*, 137 (2014), pp. 3355-3370

[131] Dudai Y. The neurobiology of consolidations, or how stable is the engram? *Ann. Rev. Psychol.*, 55 (2004), pp. 51-86

[132] Bramham CR, Messaoudi E. BDNF function in adult synaptic plasticity: the synaptic consolidation hypothesis *Prog. Neurobiol.* 76 (2) (2005), pp. 99-125

consolidation, where hippocampus-dependent memories become independent of the hippocampus over a period of weeks to years.[133]

78. One of the most troubling concomitants of aging for many individuals is the impairment of learning and memory which often occurs even with "normal" aging. Neuronal changes occur during aging and contribute to learning and memory deficits. This includes calcium-mediated currents, as related to acquisition of hippocampus-dependent behavioral tasks and to age. By extension these calcium increases are relevant to understanding the mechanisms of Alzheimer's disease, a disease whose greatest risk factor is age and that has grown in importance as the population is living longer on average, as well as the normal cognitive decline in an aged, but otherwise healthy, individual. I understand that Prevagen is a dietary supplement that is marketed to healthy adults who have concerns about the normal aging process and its potential effect on memory and cognitive functioning. This type of proactive, safe and low-cost therapeutic approach makes good sense. Even if an individual is at no risk of developing Alzheimer's disease or another form of memory loss or cognitive degeneration, safe and low-cost dietary supplements can provide benefits. In the case of Prevagen, the clinical data suggests that it is safe and does in fact provide benefits.

XII. NON-CLINICAL (ANIMAL) STUDIES:

79. During ischemia, the deprivation of blood flow and oxygen to the brain results in excessive calcium influx through glutamate receptors, which can rapidly trigger cell death. One way that neurons protect themselves from the toxic effects of calcium is to buffer the calcium with

[133] C.J. Rodriguez-Ortiz, F. Bermudez-Rattoni Memory Consolidation or updating consolidation (2007) Bermudez-Rattoni (Ed.), "Neural Plasticity and Memory: From Genes to Brain Imaging" CRC Press/Taylor & Francis, Boca Raton (FL) Chapter 11

calcium binding proteins (CaBPs)[134] and, in animal studies, apoaequorin has been shown to beneficially support neuronal cells via calcium modulation.[135] Based on *in vitro* and *in vivo* animal studies[136] involving apoaequorin in addition to other studies involving large proteins that bind calcium[137] there is scientific potential to enhance memory and cognitive function in humans via calcium binding. Controlled studies over a 32-day period with apoaequorin in aged canines demonstrated a statistically significant cognitive enhancement.[138]

80. Pretreatment with apoaequorin specifically, has been reported to protect the rat brain slice hippocampal neurons from oxygen-glucose deprivation[139] and has led to studies of the effects of an oral supplement containing apoaequorin (10 mg/day) on verbal learning in older humans.[140]

XIII. MEMORY AND CALCIUM SIGNALING

81. One of the primary hypotheses for the cause of cognitive decline involve the dysregulation of calcium in the hippocampus. The hippocampus is part of the limbic system, and

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[134] Detert JA, Heisler JD, Hochstetter EL, et al. Neuroprotection of hippocampal Ca+ 1 neurons from ischemic cell death using the calcium-binding protein aequorin. "Society for Neuroscience Abstracts." 2009

[135] Pretreatment with apoaequorin protects hippocampal CA 1 neurons from oxygen-glucose deprivation. 11, 2013, PLoS One, Vol. 8, p. e79002

[136] Detert JA, Adams EL, Lescher JD et al. Pretreatment with Apoaequorin Protects Hippocampal CA1 Neurons from Oxygen-Glucose Deprivation. PLoS ONE 2013 8(11): e79002. doi:10.1371/journal.pone.0079002

[137] Borger E, Herrmann A, Mann DA etal. The Calcium-Binding Protein EFhd2 Modulates Synapse Formation In Vitro and Is Linked to Human Dementia *J Neuropathol Exp Neurol* Volume 73, Number 12, December 2014 1166-1182

[138] Milgram NW, Landsberg G, Merrick D et al. A novel mechanism for cognitive enhancement in aged dogs with the use of a calcium-buffering protein *J Vet Behavior* 10 (2015) 217- 222

[139] Detert JA, Adams EL, Lescher JD et al. Pretreatment with apoaequorin protects hippocampal CA1 neurons from oxygen-glucose deprivation PLoS One (2013) 10.1371/journal.pone.0079002

[140] D.L. Moran, M.Y. Underwood, T.A. Gabourie et al. Effects of a supplement containing apoaequorin on verbal learning in older adults in the community 2016 *adv mind body med.* 30, pp. 4-11

plays important roles in learning and the consolidation of information from short-term memory to long-term memory.[141]

82. Dysregulation of calcium occurs progressively and naturally for many in the aging process, and has been shown to be a common precursor for cognitive decline and Alzheimer's disease.[142] [143] [144] [145] [146] Prevagen and/or its substrates and/or its metabolites may exert pharmacological activity through calcium signaling binding sites. In terms of calcium binding sites, cholesterol binding domains and pore lining regions -- the active ingredient in Prevagen (apoaequorin) -- is very similar to calmodulin, (a intracellular multifunctional intermediate calcium-binding messenger protein) which plays a primary factor in memory consolidation.[147] In a similar vein, the FDA- approved drug memantine (Namenda) is an uncompetitive antagonist to the N-methyl-D-aspartate (NMDA) receptor that is now thought to help patients with Alzheimer's disease chiefly or in part by limiting calcium entry into neurons through the NMDA receptors.[148]

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[141] Haass C, Selkoe DJ. Soluble protein oligomers in neurodegeneration: Lessons from the Alzheimer's amyloid B-peptide. *Nat. Rev. Mol. Cell Biol.* 2007, 8, 101–112

[142] Green, K. Calcium in the initiation, progression and as an effector of Alzheimer 's disease pathology. *J Cellular Molec Med*, 2009, 13(9A), 2787-2799

[143] Gibson GE, Peterson C. Calcium and the aging nervous system. *Neurobiol Aging*. 1987 8, 329- 343

[144] Khachaturian ZS. The role of calcium regulation in brain aging: re-examination of a hypothesis. *Aging* (Milano). 1987 1, 17- 34

[145] Disterhoft JF, Moyer JR, Thompson LT. The calcium rationale in aging and Alzheimer's disease. Evidence from an animal model of normal aging. *Ann. N.Y. Acad. Sci*. 1994 747, 382- 406

[146] Kawamoto EM, Vivar C, Camandola S. Physiology and pathology of calcium signaling in the brain. *Front. Pharmacol*. 2012 3. Article 61

[147] Limback-Stokin K, Korzus E, Nagaoka-Yasuda R, et al. Nuclear calcium/calmodulin regulates memory consolidation. *J Neurosci*., 24 (2004), pp. 10858-10867

[148] https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021487s010s012s014,021627s008lbl.pdf

83. Synaptic plasticity, long-term potentiation, and long-term depression are dependent on calcium signaling and all are affected by age.[149] Electrophysiological studies in the rat hippocampus (which plays important roles in the consolidation of information from short-term memory to long-term memory, and in spatial memory that enables navigation) have shown that biomarkers of aging that are mediated by calcium, such as a larger amplitude after hyperpolarization, reflect increased intracellular calcium and correlate temporally with the emergence of cognitive decline.[150]

84. Apoaequorin has been shown in preliminary laboratory study to decrease cell death due to ischemia by 55% in aged hippocampal cells, ostensibly via calcium signaling, but possibly through another mechanism.[151] This study establishes a foundation for a relationship between Prevagen and improvements on quantitative measures of cognitive function.

85. Overall, various human, animal and basic science studies along with Prevagen's binding sites are indicative of Prevagen having a positive therapeutic utility in delaying or modifying the decline, via calcium buffering or other mechanism, with regards to the cognitive functioning associated with aging.

XIV. MADISON MEMORY STUDY CLINICAL PROOF OF CONCEPT

86. I have reviewed and agree with the published findings of the Madison Memory Study (MMS). There have been no contradicting published clinical studies that I found during a

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[149] Foster TC, Kumar A. Calcium dysregulation in the aging brain. *Neuroscientist*. 2002 8. 297- 301

[150] Gane JC, Sama MM, Landfield PW, Thibault 0. Early and simultaneous emergence of multiple hippocampal biomarkers of aging is mediated by Ca2·- induced Ca2+ release. *J. Neurosci*. 2006 26. 3482- 3490

[151] POSTER PRESENTATION "*Detert, J., Schmidt , M., Kampa, N., Tao, P., & Moyer, J. (2007). Apoaequorin protects adult and aging hippocampal CA 1 neurons from ischemic cell death. Poster presented at the Society for Neuroscience Conference, San Diego , CA*"

thorough search of Medline. The MMS study reported statistically significant improvements in clinical findings, specifically executive functioning and delayed recall.[152] This study also found improved scores of executive function over three months in the Groton Maze Learning task. Additionally, the Prevagen group significantly improved delayed recall scores compared to placebo.

87. In a measure of learning, the Prevagen arm also significantly reported better performance than the placebo group. Prevagen users also improved their ability to recall items on a grocery shopping list. In a sub-group analysis of participants experiencing the least memory impairment according to the AD8 Dementia Screening Interview administered at baseline, the Prevagen arm experienced even greater improvement in delayed recall. Prevagen appeared to be well-tolerated with only one drop-out in each arm due to an adverse event.

88. The clinical results demonstrate that Prevagen (apoaequorin 10mg) was statistically significantly better than placebo at improving domains of cognitive function such as learning and delayed recall after 90 days. For adults with memory concerns, Prevagen is a safe, effective and well-tolerated supplement to help with cognitive function. These results suggest adults just beginning to experience some memory lapses may benefit most from Prevagen.

XV. SUMMATION

89. In sum, age-related memory loss has no convincing FDA-approved pharmacological cure. Existing drug treatments are few and have only been minimally and/or temporarily effective. The dietary supplement Prevagen appears to be able to be safely

[152] Hume AL. Apoaequorin for memory enhancement? Pharmacy Today (Sept. 2015), p. 38

administered by the lay public at its recommended doses. The FDA has chosen not to regulate the thousands of supplements such as Prevagen. Even if the FDA did decide to regulate dietary supplements, I would expect that it would allow the use of Prevagen based on the totality of the scientific evidence discussed herein, and the lower standard needed for dietary supplement substantiation.

90. Stating something just won't work based on outside observational data by non-experts and simply dismissing positive clinical and non-clinical findings adds nothing to the academic argument. Science progresses when experts in the relevant field debate the issues relating to the subject at hand by analyzing the data. Prevagen should be permitted to be sold as a nutritional supplement, with the Challenged Claims, based on its existing *in vivo* and *in vitro* findings.

91. Said otherwise, it is easy to stand back and declare why something wouldn't or shouldn't happen. Examples of things which people thought were "impossible" include: heavier-than-air-flight[153] or the seemingly unexplainable physics of objects spinning through zero gravity (see video reference).[154] As the old English idiom states: "The proof is in the pudding[155]" or in this case the proof of concept (causality) is reflected in the published positive statistically significant clinical and non-clinical results, and an entirely plausible pharmacological mechanism

[153] https://www.newscientist.com/article/mg16622437-900-taking-flight/

[154] What… is going on with this spinning object in zero gravity? https://www.sciencealert.com/watch-wtf-is-going-on-with-this-object-spinning-in-zero-gravity

[155] https://idioms.thefreedictionary.com/proof+is+in+the+pudding "*Prov. You cannot be sure that you have succeeded until you have examined the result of your efforts*"

of action and putative calcium- connected disease pathology. These include the following facts that:

1) Calcium plays a basic and critical role in learning, and memory in the human brain.

2) Dysregulated, excess neuronal/hippocampal calcium has objectively been shown in the literature whether by cause or as a biomarker in playing a negative role in memory formation and several memory-related conditions.

3) Prevagen has been shown to have four different calcium binding sites, each of which may work **a)** in combination or **b)** separately to bind excess calcium.

4) Prevagen and/or its substrates and/or its metabolites may exert pharmacological activity through calcium signaling binding sites.

5) Prevagen has the potential to be actively transported in part or whole through **a)** the gut through or **b)** into the CNS via active transport via its three separate cholesterol binding sites.

As such, it is my opinion, within a reasonable degree of scientific certainty, that Dr. Berg's opinion regarding the lack of pharmacological evidence is contrary to the evidence and that there exists competent and reliable scientific evidence to support the Challenged Claims made regarding Prevagen.

I reserve the right to review any additional materials that become available in this matter and to amend my opinion accordingly.

Dated: July 15, 2021

D. Gortler

Digitally signed by D. Gortler
Date: 2021.07.15 09:27:31 -07'00'

David Gortler, Ph.D.

Exhibit A

David Gortler, Pharm.D. FCCP

Curriculum Vitae

Contact Information

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E-mail (routine/daily)**:** david.gortler@gmail.com
E-mail (secure server)**:** davidgortler@protonmail.com

I have never had any social media other than Linked in

Summary

Dr. David Gortler is an **FDA regulatory science** and **FDA device and drug safety expert**.

He is a former member of the FDA Senior Executive Leadership Team who served as senior advisor to the FDA Commissioner on matters of: FDA regulatory affairs, drug safety and FDA science policy. He is former Yale University and Georgetown University didactic professor of pharmacology and biotechnology, with over a decade of academic pedagogy, as part of his nearly two decades of experience in drug development.

He had previously served as an FDA medical officer/senior medical analyst, and was personally in charge of approving new drugs and labeling changes within the FDA's Center of Drug Evaluation and Research (CDER). Prior to that, Dr. Gortler served as an investigational medicine research scientist and clinical trial principal lead at Pfizer Inc, as well as a scientific and drug safety advisor to Merck & Co, in addition to several other major pharmaceutical and medical device developers and manufacturers.

He currently serves as a senior scholar at the Ethics and Public Policy Center (EPPC) think tank in Washington DC where he co-leads the HHS/FDA Accountability Project.

Professional & Academic Experience

Senior Advisor to the FDA Commissioner **(2019 - 2021)**

- Hired to advise the FDA Commissioner on matters of regulatory affairs, drug safety and FDA policy. Employed via the White House as a Senior Executive Service (SES) Level 2
- Was the first pharmacist/pharmacologist to *ever* be appointed as Senior Advisor to the FDA Commissioner the 120+ year history of the FDA.
- Worked closely (on a daily basis) with the FDA Commissioner and the FDA senior executive leadership team, advising on particular matters of regulatory affairs, FDA policy and drug safety
- Spearheaded policy on advancing state-of-the-art human cell micro-plating technology to replace outdated FDA-mandated pre-clinical (animal) testing required for faster and safer drug approval
- Researched and wrote public opinion articles for The Office of the Commissioner
- Advanced new policy to favor environmentally-responsible US manufacturing of generic drugs, APIs and precursors
- Implemented my privately-conceptualized company concept of "Real Time Release Testing" of Chinese and Indian drugs by lot before they are released to US pharmacies

- Lead major 2019-nCoV development related, safety and FDA regulatory policy initiatives as directed by the FDA Commissioner
- Analyzed and summarized massive FDA database sets on drug safety information from AERS / FAERS / MAUDE and VAERS
- Provided novel, well-researched, sound, data-driven, state-of-the art guidance, advice and expertise, to the FDA Commissioner and other members senior executive leadership team on advancing and improving FDA and public health matters which include, but were not limited to:

Advanced manufacturing	Drug testing/drug quality	Mail-order pharmacy regl'n
Asian/Indian drug quality	Emrg. vaccine authorizations	New FDA policy initiatives
Drug billing/transparency	FDA recall authority	State-of-the-art preclinical dev.
Drug safety /Device safety	**FDA regulatory affairs**	Pandemic opioid use/MAT
Drug supply onshoring DOD	Healthcare policy	Release testing RTRT & QC

Executive Office of the President (EOP) Trade Office **(2020)**

- Worked extensively and directly as an advocate of the FDA and public health at the White House with:

  1) Presidential special advisors,
  2) Presidential special assistants
  3) Presidential departmental directors and
  4) Presidential senior advisors
  on matters related to HHS/FDA policy, public health and American manufacturing re-onshoring and state-of-the art methodology to improve and expedite drug manufacturing and approvals.
- Personally conceived of and assisted in the composition of multiple HHS/FDA presidential executive orders to lower drug pricing, increase drug safety, increase drug pricing transparency.

Ethics and Public Policy Center (EPPC) Institute. **HHS/ FDA Policy Fellow (2021 – current)**

FDA policy subject matter expert who helped establish and run the FDA branch of the *EPPC's HHS Accountability Project* holding FDA officials accountable and researching and writing scientifically-backed op-ed articles and conducting original research on public health matters such as animal testing, FDA policy, the opioid crisis, vaccine safety and drug safety.

Heartland Institute. **Senior Healthcare and FDA Policy Fellow (2014 – 2019)**

- Advisor at think tank on FDA and healthcare policy issues including drug importation, freedom-to-choose healthcare, patient compliance, generic drug quality from Chinese and Indian importers, drug safety and practical improvements to the drug development process without compromising scientific integrity.

Valisure LLC, Yale Science Park, New Haven, CT **Chief Medical Officer (2015 - 2019)**

Conceived of and founded the world's first "*Analytical Pharmacy*"

- Prepared and provided formal presentations of clinical and pharmacology data, as well as comprehensive explanations of current medical literature relating to specific issues or cases, for non-medical professionals and other lay individuals.

Independent Pharmacology/Device Safety Consulting **(2005 – 2007 & 2012 – 2019)**

- Researched and delivered expert services in multiple, complex multibillion-dollar lawsuits, including comprehensive interpretations of scientific publications related to vascular occlusion and thrombosis based on clinical pharmacology and basic science research, independent and comprehensive examinations of medical literature pertaining to cases, and independent professional opinions (based on detailed study) in heavily referenced publication-style report.
- Managed wide variety of complex consultations for investors, pharmaceutical companies, and attorneys, including various safety and efficacy analyses of clinical study proposals, reports, product labeling NDAs, End of Phase 2 go/no go criteria, new protocols, and protocol amendments.
- Prepared summary presentations and served as a Subject Matter Expert (SME) and advisor on complex regulatory FDA issues including FDA law, clinical trial regulatory affairs, drug labeling, orphan drug designations, drug safety, drug importation and manufacturing, clinical trial design, and clinical trial ethics.
- Provided attorney/witness preparation and personally provided expert depositions for a wide range of legal cases, from small physician malpractice suits and patent declarations, to multibillion-dollar class-action lawsuits.

Peer-Reviewed Journal Editorial Boards:

Advances in Investigational Pharm. and Therapeutic Med.	Editor-in-Chief (2016 – 2019)
Journal of Pharmacology and Clinical Toxicology	Editorial Board Member (2012 – 2019)
Journal of Drug Research and Development	Editorial Board Member (2013 – 2019)
Chronicles of Pharmaceutical Science	Editorial Board Member (2016 – 2019)
Research Journal of Addiction Med. and Rehab.	Editorial Board Member (2016 – 2019)

Ted Cruz 2016 Presidential Campaign Healthcare/FDA Policy Advisor (2016)

- Advised candidate on FDA policy, drug safety, FDA regulatory affairs, private insurance architecture proposals, and issues relating to **drug pricing**, pharmaceutical importation, "Right-to-Try" legislation, and accelerated approval for orphan drugs and compassionate use designations.

US Food and Drug Administration Senior Medical Analyst/Medical Officer (2007 – 2011)

- Lead reviewer responsible for safety and efficacy analyses of clinical study protocols, reports, product labeling BLAs, DNAs, INDs, new protocols, and protocol amendments.
- Lead medical officer for the SEARCH trial, *Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine*, addressing the safety and efficacy of simvastatin 80mg.
- Lead efficacy medical officer for the ultimate FDA approval of Livalo (piavastatin) NDA.
- Prepared written summaries and formal presentations concerning safety and efficacy of protocols and package labeling for interdisciplinary reviewers and division directors.
- Advised major pharmaceutical companies on suitability of drug development plans
- Used state-of-the art science to ensure clinical trials were adequate, well-controlled, and sufficient to support the efficacy and safety of drugs under investigation.

- Reviewed post-marketing safety reports, databases, and safety submissions to detect potential issues requiring further evaluation or product labeling changes.
- Compiled data to prepare special reports on the work of the Division of Metabolism and Endocrinology Products and analyzed additional pertinent data relating to FDA programs.
- Assessed new drug applications, supplements, and pre-clinical applications based on the most recent FDA guidance documents and the Code of Federal Regulations.

Georgetown University Associate Professor of Pharmacology (2009 – 2014)

- Professor, lecturer, research advisor, and thesis advisor to graduate level Pharmacology and Medical students, including Ph.D. candidates, in various therapeutic areas.

Yale University Assistant Professor of Pharmacology (2004 – 2008)

- Lectured on graduate level clinical pharmacology for medical, physician assistant, and pharmacology Ph.D. students on topics including cardiology, metabolic diseases, obesity, alcohol pharmacology and neuropharmacology, drug development, and drug abuse, among others.
- Served as research advisor for medical, physician assistant, and pharmacology Ph.D. students.
- Conducted clinical investigations analyzing and standardizing drug therapy during surgical procedures including carotid endarterectomy and carotid stenting procedures.
- Conducted clinical investigations on state-of-the-art compounds with the potential to modulate endogenous cholesterol levels.
- Conducted science research exploring hemodynamic cell signaling pathways related to vascular wall thickening, inflammation, plaque stabilization, migration, and the non-random localization of atherosclerotic plaques in the vasculature.
- Served as faculty member of the Yale University Center for Bioethics, Research Ethics working group and the Research Ethics writing group.

Gaylord Hospital & Hill Health Center Clinical Coordinator (2005 – 2008)

- Operated a drug-monitoring clinic for hypercholesterolemia, hypertension, diabetes, and warfarin.
- Identified and resolved pharmacy-related patient care issues by implementing collaborative, cooperative, communicative, interdependent relationships with medical staff.
- Supervised and performed various duties in both hospital and ambulatory care settings, including recommending appropriate evidence-based therapeutic regimes based on provider diagnoses, designing and implementing evidence-based drug monitoring plans, monitoring patients' progress via laboratory assessment and physical assessments, making dosing decisions based on progress, and integrating thorough and effective communication techniques for patient interviews to assess patients' pharmaceutical history and use.
- Responsible for Medicare billing reimbursement paperwork, cost-saving implementations, and other budget and billing duties.
- Responsible for covering director's duties and meetings in his absence.

Pfizer Inc. **Investigational Medicine Research Scientist (2001 – 2005)**

- Responsible for designing and implementing state-of-the-art clinical pharmacology studies for multiple early and full development compounds.
- Personally designed and composed Phase 1 and 2 protocols and study reports for first in-human studies, multiple dose studies, food effect studies, dose escalation studies, drug interaction studies, and dose bioequivalence studies.
- Responsible for Contact Research Organization (CRO) selection, contract negotiations, study initiation, supervision, clinical safety monitoring, and management.

Education

Yale University **Vascular and Cardiovascular Medicine Research Fellowship (1999 – 2002)**

- Studied atherosclerosis, diabetic levels of glucose isomers and their effects on endothelial and smooth muscle cells.
- Studied red wine polyphenols (with emphasis on resveretrol and quercetin) and their role in atherosclerotic disease.
- Studied smooth muscle migration and cell analysis as related to atheroma formation.
- Studied cyclic strain induced activation of pro-survival cascades, and its effects on the phosphorylation of AKT and BAD, the rate and extent of apoptosis, and the transcription factor NF[k]B in bovine aortic endothelial cells and bovine aortic smooth muscle cells.
- Studied the significance of cytoskeleton integrity in mechanical stress induced signal transduction in bovine aortic endothelial cells, including the cyclic strain induced activation of the GTPase RhoA and the effects of cytochalasin B on cyclic strain induced activation of MAPK.
- Studied the effects of galvanotaxis on vascular endothelial and smooth muscle cells.
- Served as clinical research investigator and coordinator in charge of screening patients upon verification of diagnosis.
- Applied GCP standards for all patient follow-ups and monitored safety and efficacy parameters.
- Served as primary or secondary contact at Yale University for several Phase 3 investigational drug trials.
- Responsible for protocol adherence, study drug accountability, compliance assessments, and adverse event assessment.
- Responsible for regulating compliance with investigational compound sponsor and the University Human Investigation Committee.
- Designed and conducted research projects in exploring the molecular mechanisms of hypertension and diabetes in association with cholesterol plaque formation and intimal hyperplasia as related to hemodynamics.

Yale-New Haven Hospital Postdoctoral Special Residency (1999 – 2000)
Clinical and Investigation Drug Information Residency (ASHP Accredited)

- Performed extensive literature research on complex questions regarding drugs and pharmacotherapy.
- Assisted Yale University Investigational Drug Service with managing more than 200 drug trials.
- Responsible for providing Yale physicians with information on medication use, including drug-drug interactions, pharmacologic mechanisms, and unapproved uses, among other information.

Columbia Presbyterian Hospital System Postdoctoral General Residency (1998 – 1999)
General Clinical Pharmacy Practice Residence (ASHP Accredited)

- Completed general residency with special emphasis in cardiac and psychiatric pharmacology.
- Completed residency project on *Standardizing Hyperlipidemia Treatment in Postoperative Cardiac Patients*. Meta-analysis cohort funded with grant from Merck Pharmaceuticals.
- Performed twice-weekly clinic and patient assessments with appropriate dosage and lifestyle recommendations.
- Served as Pharmacy and Therapeutics Committee member to address disease state management protocol and hospital formulary issues.
- Served as Investigational New Drug Review Committee member and worked with private industry to set up clinical trials in several patient populations.
- Served as Anticoagulation and Hypertension clinic team member.
- Served as Assistant Clinical Instructor at Rutgers College of Pharmacy Department of Pharmacy Practice and the Bergen Community College Department of Nursing.

University of Arizona, College of Pharmacy Pharm.D. (1994 – 1998)

- Doctor of Pharmacy conferred 1998

Professional Memberships and Licensures

Fellow of the American College of Chest Physicians	FCCP (2007 – Present)
Fellow of the American Society of Consultant Pharmacists	FASCP (2005 – 2011)
Drug Information Association	(2002 – 2005)
Fellow of the American Society of Clinical Pharmacology and Therapeutics	(2003 – Present)
American Society of Health System Pharmacy Member	(1994 – 2002)
Arizona State Board of Pharmacy License	#511993
Connecticut State Board of Pharmacy License	#09257
Pharmacotherapy National Provider Identifier (NPI)	1962692681

Hobbies and Interests

Vintage firearms
Automobile restoration
Home improvement
Animal rescue
MSSQL programming

Gortler Case History (represented the underlined client)

Matter:	Aaron Young v. Olympus America, Inc.
Responsibility:	Expert report, device safety. Deposition
Date:	2021
Matter:	Elsebai v. Bayer et al.
Responsibility:	expert report, pharmacology, regulatory affairs
Date:	2019
Matter:	Epic Pharma LLC v. Philadelphia Truck Lines, Inc. et al.
Responsibility:	Expert report on drug safety
Date:	2019
Matter:	Viable Research Management / Alas Science Clinical Research v. Ezekiel and Olga Martin
Responsibility:	Expert report and deposition
Date:	2019
Matter:	Jenkins v. Gass, M.D., Graves-Gilbert Clinic and CareFusion
Responsibility:	Expert report
Date:	2019
Matter:	Pharma-Bio v. Eisai, Inc.
Responsibility:	Expert report and deposition
Date:	2019
Matter:	Bigler v. Olympus America, Inc.
Responsibility:	Expert report on device safety with deposition
Date:	2018
Matter:	Keith, et al. v. Ferring Pharmaceuticals
Responsibility:	Expert report
Date:	2018
Matter:	Schoulee Cones, et al., v. Parexel International Corp.
Responsibility:	Expert report on FDA regulatory affairs and deposition
Date:	2018
Matter:	Abigail Schmitt v. Genesys Regional Medical Center
Responsibility:	Expert report and deposition
Date:	2018
Matter:	Mallinckrodt Inc. v. Citron Research
Responsibility:	Expert report
Date:	2017

Matter:	KBC Asset Management NV, et al. v. Aegerion Pharmaceuticals, Inc.
Responsibility:	Expert report and deposition
Date:	2017